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(54) Title: NONCLASSICAL PYRROLO[2,3-D]PYRIMIDINE ANTIFOLATES

(57) Abstract

Nonclassical pyrrolo[2,3-d]pyrimidine antifolates are described and claimed. Also described and claimed is a rapid analog process which enables a quick work-up of the antifolate which avoids costly and time-consuming chromatographic separation techniques. Also described and claimed are methods of treating susceptible neoplasms with these nonclassical antifolates. Also described and claimed are methods of treating psoriasis and arthritis with these nonclassical antifolates.

Applicants: Arlindo L. Castelhano, et al.
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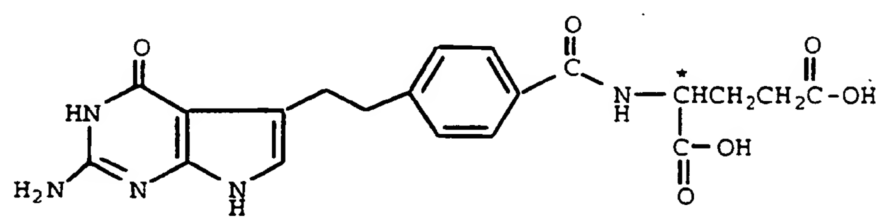
NONCLASSICAL PYRROLO[2,3-D]PYRIMIDINE ANTIFOLATES

The invention relates generally to the fields of pharmaceutical and synthetic organic chemistry. Specifically, the invention relates to the field of antifolate compounds which are useful in the treatment of various diseases.

Through a mechanism of enzyme catalyzed reactions, folic acid is used by a number of cells to fuel cell replication. Antifolate compounds mimic folic acid and its derived cofactors when taken up in a cell. Antifolates interact with various folate requiring enzymes in cells to eventually cause the inhibition of cell replication. Antifolate compounds are known to be useful in the treatment of cancer by providing a means to terminate the growth of malignant cells.

Classical antifolate compounds, such as the multi-targeted antifolate LY 231514 (N-[4-[2-(2-amino-3H-4-oxo-pyrrolo[2,3-D]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid)



* the configuration around this carbon is L

(U.S. Patent No. 5,334,932), have a glutamic acid moiety in the natural or "L" configuration on one end of the molecule. Upon entry of a classical antifolate into a cell, the enzyme folylpolyglutamate synthetase (FPGS)

causes a polyglutamation reaction to take place at the glutamic acid end of the antifolate. The polyglutamated antifolate then can interact with other folate requiring enzymes such as dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyl transferase (GARFT) and/or thymidylate synthase (TS). Interaction of the polyglutamated antifolate with DHFR and/or GARFT and/or TS and/or other folate utilizing enzymes eventually leads to inhibition of cell replication.

It has been observed that efficacy, in terms of inhibiting cell replication, of classical antifolates can decrease with continued use of the antifolate. One possible explanation for this observed phenomenon is that malignant cells become resistant toward classical antifolates through impaired (less efficient) polyglutamation reaction(s). As a polyglutamated antifolate interacts better with folate requiring enzymes than does a monoglutamated antifolate, this lack of polyglutamation could be sufficient to account for the decline in efficacy.

One way of increasing efficacy, in terms of inhibiting cell replication, is to provide an antifolate that does not contain a terminal glutamic acid moiety in the "L" configuration, thus avoiding the need for polyglutamation with FPGS. The difficulty in providing such a compound is that the compound, in order to be effective in inhibiting cell replication, must still be able to effectively inhibit with other folate requiring enzymes even though it is not polyglutamated.

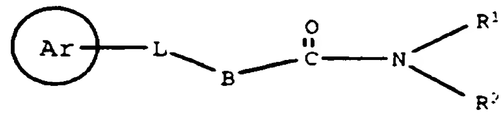
The concept of using a non-polyglutamatable inhibitor was suggested in 1983 as an approach to the design of novel DHFR inhibitors targeted against FPGS deficient tumors. See "Methotrexate Analogues. 20. Replacement of Glutamate by Longer-Chain Amino Diacids: Effects on Dihydrofolate Reductase Inhibition, Cytotoxicity, and in Vivo Antitumor Activity", Rosowsky, *et al.*, J. Med. Chem., (1983), 26, 1719-1724.

In addition, several derivatives of folic acid in which the terminal L-glutamate moiety is replaced by L-ornithine have been shown to be effective inhibitors of FPGS in "Synthesis and Biological Evaluation of N^{α}-(5-Deaza-5,6,7,8-tetrahydropteroyl)-L-ornithine", Singh, *et al.*, J. Med. Chem., (1992), 35(11), 2002-6.

Non-polyglutamatable inhibitors were also described for the GARFT enzyme in "First Use of the Taylor Pteridine Synthesis as a Route to Polyglutamate Derivatives of Antifolates. 46. Side Chain Modified 5-deazafolate and 5-deazatetrahydrofolate Analogs as Mammalian Folypolyglutamate Synthetase and Glycinamide Ribonucleotide Formyl Transferase Inhibitors: Synthesis and in Vitro Biological Evaluation", Rosowsky, *et al.*, J. Med. Chem., (1992), 35(9), 1578-88.

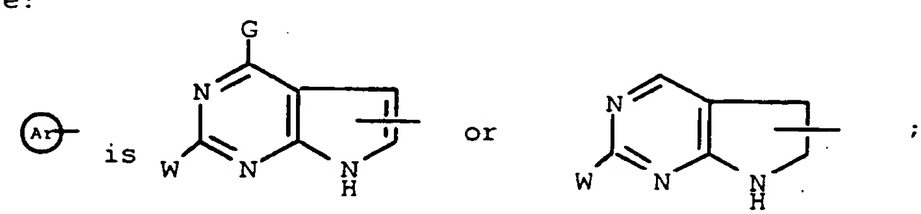
What are needed are pyrrolo[2,3-d]pyrimidine non-classical antifolates, configured such that they are non-polyglutamatable, but also configured such that they can inhibit folate requiring enzymes.

The first aspect of the invention is a compound of formula (III):



(III)

where:



W and G are independently -H, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, $-NR^3R^4$, $-SR^5$, $-OR^6$ or halo,

R^3 and R^4 are independently -H, optionally substituted C_1-C_6 alkyl, or a suitable amino protecting group, or together N, R^3 and R^4 are a phthalimido group,

R^5 is -H, optionally substituted C_1-C_6 alkyl or a suitable thiol protecting group, and

R^6 is -H, optionally substituted C_1-C_6 alkyl or a suitable hydroxy protecting group;

L is $-R^7-Q_{(a)}-$, where

R^7 is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH{=}CH-$, $-C{\equiv}C-$, $-CH{=}CHCH_2-$, $-CH_2CH{=}CH-$, $-CH_2C{\equiv}C-$ and $-C{\equiv}CCH_2-$, and when R^7 is not $-C{\equiv}C-$, R^7 may be substituted with C_1-C_2 alkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 hydroxyalkyl wherein the H on the hydroxy moiety has been replaced with a hydroxy protecting group,

Q is -O-, -S- or $-NR^8-$,

a is zero or 1,

R^8 is -H, optionally substituted C_1-C_3 alkyl, alkoxycarbonyl or phenoxycarbonyl;

B is selected from the group consisting of:

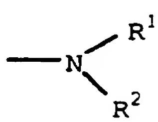
optionally substituted 1,2-, 1,3-, or 1,4-phenylene,

optionally substituted 2,3-, 2,4-, or 2,5-thiophenediyl,

optionally substituted 2,3-, 2,4-, or 2,5-furandiyl,

optionally substituted 1,2-, 1,3-, or 1,4-cyclohexanediyl, and

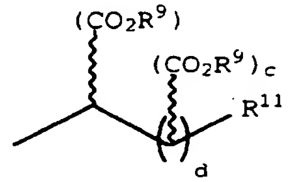
optionally substituted $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$,



is

A) an α-amino acid residue, selected from the group consisting of -alanine, -arginine, -asparagine, -aspartic

acid, -cysteine, -cystine, -glutamine, -glycine, -histidine, -hydroxyproline, -isoleucine, -leucine, -lysine, -methionine, -phenylalanine, -proline, -serine, -threonine, -tryptophan, -tyrosine and -valine, **OR**

B) R^1 is , and R^2 is -H,

where

c is zero or 1,

d is zero, 1, 2, 3, 4, 5 or 6,

R^9 are each independently -H or a suitable carboxylic acid protecting group, and

R^{11} is

i) $-COOR^{10}$, where R^{10} is -H, optionally substituted alkyl or a suitable carboxylic acid protecting group, or

ii) -H, -OH, 1-carboxyeth-1-yl, optionally substituted C_1-C_6 alkyl, optionally substituted cycloalkyl, carboxycycloalkyl, optionally substituted aryl, carboxyaryl, optionally substituted heteroaryl, optionally substituted alkyl(aryl), optionally substituted C_1-C_6 alkoxy, optionally substituted polycyclic, optionally substituted 5-tetrazolyl, or

iii) $-(CH_2)_e-U$

where: e is 0, 1, 2, 3 or 4,

U is $-O-CH_2-COOH$, $-S-CH_2-COOH$ or $-NR^{12}R^{25}$,

R^{12} is -H or a suitable amino protecting group,

R^{25} is benzoyl or carboxybenzoyl, or

iv) $-(CH_2)_e-T$, where

e is as above, T is phthalimido, $-CO_2R^{10}$, $-SO_{(g)}X$, $-NR^{13}R^{14}$, $-CONR^{13}R^{14}$, $CONHSO_2R^{15}$, $-PO_3H_2$ or -CO-α-amino acid residue,

R^{10} is as above,

g is zero, 1, 2 or 3, providing that

when g is zero, 1 or 2, X is optionally substituted C_1-C_6 alkyl, and when g is 3, X is -H,

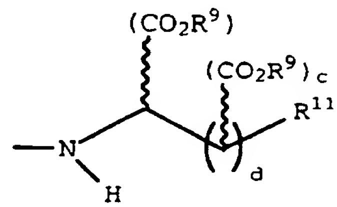
R^{13} is -H,

R^{14} is -H, optionally substituted C_1-C_6 alkyl, optionally substituted C_5-C_7 aryl, $-CHR^{16}NR^{15}R^{16}$, $\overset{O}{\overset{\|}{C}}$-aryl, or a suitable amino protecting group,

R^{15} is optionally substituted alkyl, optionally substituted aryl, benzyl or carboxyaryl, and

each R^{16} is independently -H or optionally substituted alkyl, and each α-amino acid residue is as above;

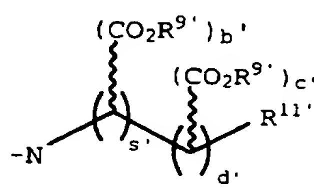
providing that all of R^{11} is so configured such that



, is not D- or L-glutamic acid, -alanine, -arginine, -asparagine, -aspartic acid, -cysteine, -cystine, -glutamine, -glycine, -histidine, -hydroxyproline, -isoleucine, -leucine, -lysine, -methionine, -phenylalanine, -proline, -serine, -threonine, -tryptophan, -tyrosine or -valine;

OR

C) R^1 is



, and R^2 is -H,

where s', b' and c' are independently zero or 1,

d' is zero, 1, 2, 3, 4, 5 or 6,

each $R^{9'}$ is independently -H or a suitable carboxylic acid protecting group,

$R^{11'}$ is

i) $-COOR^{10'}$, where $R^{10'}$ is -H, optionally substituted alkyl or a suitable carboxylic acid protecting group,

ii) -H, -OH, 1-carboxyeth-1-yl, optionally substituted C_1-C_6 alkyl, optionally substituted cycloalkyl, carboxycycloalkyl, optionally substituted aryl, carboxy aryl, optionally substituted heteroaryl, optionally substituted aryl(alkyl), optionally substituted alkoxy, optionally substituted polycyclic, optionally substituted 5-tetrazolyl, or

iii) $-(CH_2)_{e'}-U'$,

where: e' is zero, 1, 2, 3 or 4,

U' is $-O-CH_2-COOH$, $-S-CH_2-COOH$, or $-NR^{12'}R^{25'}$,

$R^{12'}$ is -H or a suitable amino protecting group,

$R^{25'}$ is benzoyl or carboxybenzoyl,

iv) $-(CH_2)_{e'}-T'$,

where e' is as above,

T' is phthalimido, $-CO_2R^{10'}$, $-SO_{(g')}X'$, $-NR^{13'}R^{14'}$, $-CONR^{13'}R^{14'}$, $-CONHSO_2R^{15'}$, $-PO_3H_2$ or -CO-α-amino acid residue, where

$R^{10'}$ is as above,

g' is zero, 2 or 3, providing that

when g' is zero or 2, X' is optionally substituted C_1-C_6 alkyl, and when g' is 3, X' is -H,

$R^{13'}$ is -H,

$R^{14'}$ is -H, optionally substituted C_1-C_6 alkyl, optionally substituted C_5-C_7 aryl, $-CHR^{16'}NR^{15'}R^{16'}$, $-\overset{O}{\overset{\|}{C}}$-aryl, or a suitable amino protecting group,

$R^{15'}$ is optionally substituted alkyl, optionally substituted aryl, benzyl or carboxyaryl, and

each $R^{16'}$ is independently -H or optionally substituted alkyl;

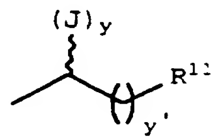
OR

D) R^1 is optionally substituted C_3-C_{20} cycloalkyl or C_3-C_{20} carboxycycloalkyl, and

R^2 is -H;

OR

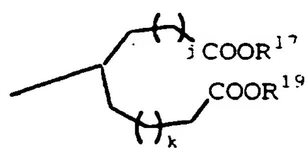
E) R^1 is



where J is optionally substituted 5-tetrazolyl or optionally substituted C_1-C_6 alkyl, y is zero or 1, y' is zero, 1, 2, 3, 4, 5 or 6 and R^{11} is as above, and

R^2 is -H;

OR

F) R^1 is  , and R^2 is -H,

where

j is zero, or an integer from 1 to 10,

k is zero, or an integer from 1 to 10,

R^{17} and R^{19} are independently -H or a suitable carboxylic acid protecting group;

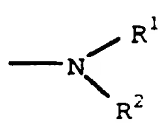
OR

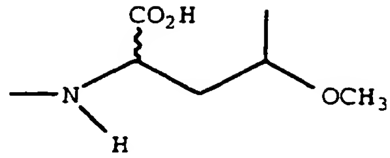
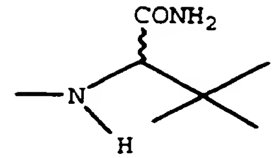
G) R^1 and R^2 are both $-(CH_2)_n-COOR^{17}$, where

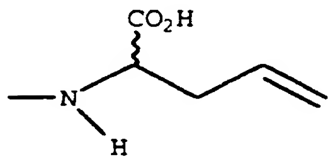
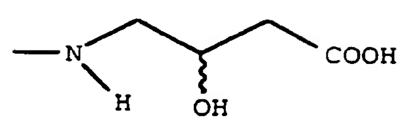
n is zero, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and

R^{17} is as defined above;

OR

H)  is:

 or  or

is:  or 

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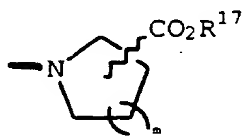
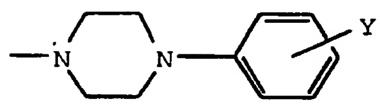
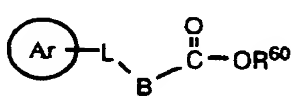
 OR 

where
m is zero, 1 or 2,
R^{17} is as above, and
Y is selected from the group consisting of halo, nitro, amino and optionally substituted alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

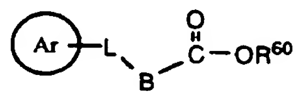
A second aspect of the invention is an active ester intermediate of formula (I):



(I)

where  , L and B have the same definitions as above, and R^{60} is selected from the group consisting of N-hydroxy-succinimidyl, N-hydroxysulphosuccinimidyl and salts thereof, 2-nitrophenyl, 4-nitrophenyl and 2,4-dichlorophenyl.

A further aspect of the invention is a process to make the compounds of formula (III), or pharmaceutically acceptable salts or solvates thereof, by reacting an active ester of formula (I):



(I)

where , L and B and R^{60} are as defined previously, with an amine of formula (II):

$$HNR^1R^2 \qquad (II),$$

where R^1 and R^2 are as defined previously, in the presence of either a silylating agent or a suitable base.

A further aspect of this invention is a continuation of the process of the second aspect of the invention, further comprising a rapid work-up procedure wherein a compound or salt of formula (III) is isolated and purified by the following procedure:

a) optionally adding a suitable diamine;
b) adding a suitable aqueous acid;
c) separating the product from its solvent;
d) preparing the product physically for collecting, washing and drying; and
e) collecting, washing and drying the product.

A further aspect of the invention is a pharmaceutical composition comprising a compound of formula (III), or a pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

A further aspect of the invention is a method of treating susceptible neoplasms in a mammal in need of such treatment comprising administering a neoplasm growth inhibiting amount of a compound of formula (III), or a pharmaceutically acceptable salt or solvate thereof, to a mammal.

A further aspect of the invention is a method of treating arthritis in a mammal comprising administering an arthritis inhibiting amount of a compound of formula (III), or a pharmaceutically acceptable salt or solvate thereof, to a mammal.

A further aspect of this invention is a method of treating psoriasis in a mammal comprising administering an arthritis inhibiting amount of a compound of formula (III), or a pharmaceutically acceptable salt or solvate thereof, to a mammal.

The term "alkyl" refers to a fully saturated monovalent group having the stated number of carbon atoms containing only carbon and hydrogen, and which may be a straight chain or branched group. This term is exemplified by groups containing from 1-6 carbon atoms, such as, but not limited to, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, t-butyl, pentyl, neopentyl, hexyl, and neohexyl. "Lower alkyl" refers to alkyl groups of from 1-3 carbon atoms.

The term "cycloalkyl" refers to a fully saturated monovalent ring which contains only carbon atoms in the ring. The "cycloalkyl" groups used herein contain at least 3 and at most 20 carbon atoms in the ring. Carboxycycloalkyl is a cycloalkyl structure that has from one to three -COOH groups in place of hydrogen(s) normally attached to carbon atoms in the ring.

The term C_1-C_6 alkoxy refers to a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom. Typical C_1-C_6 alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and the like.

The term "C_2-C_6 alkenyl" refers to a monovalent, straight or branched chain containing only two to six carbon atoms with hydrogens attached and which contains at least one double bond.

Alkoxycarbonyl is the group $RO\text{-}\overset{O}{\overset{\|}{C}}\text{-}$, where R is C_1-C_6 alkyl.

Phenoxycarbonyl is the group $PhO\text{-}\overset{O}{\overset{\|}{C}}\text{-}$, where Ph is phenyl.

α-Amino acid residues includes optionally substituted -alanine, -arginine, -asparagine, -aspartic acid, -cysteine, -cystine, -glutamine, -glycine, -histidine, -hydroxyproline, -isoleucine, -leucine, -lysine, -methionine, -phenylalanine, -proline, -serine, -threonine, -tryptophan, -tyrosine and -valine. Of these, all but glycine are chiral at the α carbon. Therefore, except for glycine, all these amino acid residues can exist in separate D and L forms or in racemic mixtures thereof. The preferred α-amino acid for the compounds of this invention is an α-amino acid in the L-configuration at the α carbon. For all of these α-amino acid residue groups the amino acid residue group is bonded to the carbonyl group of Compound III through the α amino nitrogen.

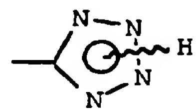
"Aryl" refers to a monovalent aromatic structure. The term "aromatic" refers to a structure containing one or more groups of carbon atoms in a cyclic array that contains clouds of delocalized π electrons above and below the plane of the atoms; furthermore, the π clouds must contain a total of (4q+2) π electrons, where q is any positive integer. For purposes of this application, these aromatic rings can contain from six to ten carbon atoms. Within this range of possible numbers of carbon atoms present, each aromatic ring must retain its aromatic character and be sterically feasible. Aromatic rings may optionally be substituted, with the proviso that only one to three of the hydrogens may be replaced.

The term "heteroaryl" refers to a monovalent aromatic structure containing from four to ten carbon atoms and at least one non-carbon atom selected from the group

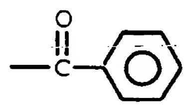
consisting of N, O or S, within the ring. Examples of heteroaryl rings include single rings, such as pyrrolidino, pyridino, pyrimidino or fused rings such as quinolo, purino, pyrido or pyrrolo[2,3-d]pyrimidino.

An aryl(alkyl) group consists of at least one aryl group substituted with at least one alkyl group.

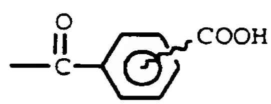
The term "halo" refers to fluoro, bromo, iodo and chloro.

A 5-tetrazolyl group is: 

The term benzoyl refers to this structure:



The term carboxybenzoyl refers to this structure:



The term "polycyclic" refers to two or more rings that share two or more carbon atoms. For purposes of this application, polycyclic compounds will be limited to monovalent ring systems that have only carbon atoms in the rings and that have either two or three rings. The number of carbon atoms in each ring varies from 4 to 8.

The term "substituted" means one to three hydrogens on the structure have been replaced with one to three moieties independently selected from the group consisting of bromo, chloro, iodo, fluoro, C_1-C_6 alkyl, $-NO_2$, aryl, difluoromethoxy, and trihaloalkyl, wherein the halo can be bromo, chloro, iodo or fluoro and the alkyl is C_1-C_3 alkyl, with the proviso that any substituted structure must be so configured that it is sterically feasible,

affords a stable structure and is capable of reacting as described herein.

The term "optionally substituted" means that the structure may or may not be substituted as described above.

A "pharmaceutically acceptable salt" may be any salt derived from an inorganic or organic acid that is suitable for administration as a drug. The salts are derived from inorganic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid (giving the sulfate and bisulfate as acid salts), nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, salicylic acid, p-toluenesulfonic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, lactic acid, o-(4-hydroxybenzoyl)benzoic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-naphthoic) acid, 3-phenylpropionic acid, trimethylacetic acid, t-butylacetic acid, laurylsulfonic acid, glucuronic acid, glutamic acid, 3-hydroxy-2-naphthoic acid, stearic acid, muconic acid and the like.

A "pharmaceutically acceptable solvate" refers to a form of a compound that has one or more solvent molecules clinging to the molecules of the compound and which form is suitable for administration as a drug. The solvent may be water, alcohol or any common organic solvent.

The term "treatment" or "treating" means administering an appropriate therapeutic or prophylactic amount of a compound of the present invention to a mammal.

The term "effective amount" means a dosage sufficient to cause a positive change in the disease state being treated. The term "positive change" will vary in

meaning depending on the patient, the disease and the treatment. For example, an effective amount of an oncolytic could be an amount that causes a reduction in the size of a cancerous tumor, or where no reduction in tumor size occurs, an effective amount of an oncolytic could be defined simply as that amount that causes a decrease in analgesic consumption for the patient suffering from cancer.

The term "protecting group" refers to a group affixed to a substrate group for the purpose of preventing the substrate group from reacting at the wrong time or with a non-targeted reagent to yield an undesired product.

The term "amino protecting group" as used in the specification refers to substituents on an amino group commonly employed to block or protect the amino functionality while allowing other unprotected functional groups on the compounds to react. Examples of such amino protecting groups include the formyl group, the trityl group, the t-butoxy carbonyl (BOC) group, the phthalimido group, the pivaloyl group, the trichloroacetyl group, the chloroacetyl, bromoacetyl and iodoacetyl groups, urethane-type blocking groups such as the benzoylmethylsulfonyl group, the 2-(nitro) phenylsulfenyl group, the diphenylphosphine oxide group and like amino protecting groups. The species of amino protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the intermediate molecule and can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amino protecting group(s). Further examples of amino protecting groups can be found in the references: J. W. Barton, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973 Chapter 2; and T. W. Greene, P.G.M. Wuts, "Protective Groups in Organic Synthesis-2nd Edition", John Wiley and Sons, New York, N.Y., 1991, Chapter 7.

The term "carboxylic acid protecting group" as used herein refers to groups commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxybenzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, methyl, ethyl, propyl, isopropyl, t-butyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4'4"- trimethoxy-trityl, 2-phenylprop-2-yl, trimethylsilyl, t-butyldimethyl-silyl, phenacyl, 2,2,2-trichloroethyl, β-(trimethylsilyl)-ethyl, β-(di(n-butyl)methylsilyl)ethyl, p-toluenesulfonyl-ethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)-prop-1-en-3-yl, and like moieties. The species of carboxylic acid protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the condition of subsequent reaction(s) on other positions of the molecule and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of these groups are found in Chapter 5 of the Barton book, "Protective Groups in Organic Chemistry", and Chapter 5 of the Greene-Wuts book, "Protective Groups in Organic Synthesis-2nd Edition".

A related term is "protected carboxy", which refers to a carboxy group substituted with one of the above carboxy protecting groups.

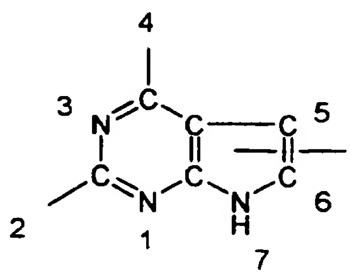
Hydroxy protecting groups include C_1-C_6 alkyl, C_1-C_6 alkylthiol, aryl, aryl(alkyl), C_2-C_6 alkenyl, C_1-C_6 alkylhalide, alkylsilyl, such as, but not limited to, trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, t-butyldimethylsilyl, arylsilyl, such as, but not limited to triphenylsilyl, tri-p-xylylsilyl,

heteroaryl alkylsilylalkyl. Further examples of hydroxy protecting groups can be found in the Greene-Wuts book.

Thiol protecting groups include benzyl, alkyl benzyl, hydroxybenzyl, acetoxybenzyl, nitrobenzyl, fluorenylmethyl, ferrocenylmethyl, diphenylmethyl, Bis(4-methoxyphenyl)methyl, 5-dibenzosuberyl, triphenylmethyl, diphenyl-4-pyridylmethyl, phenyl, 2,4-dinitrophenyl, t-butyl, 1-adamantyl, monothio, dithio and aminothioacetals, and thiazolidine. Further examples of thiol protecting groups can be found in the Greene-Wuts book.

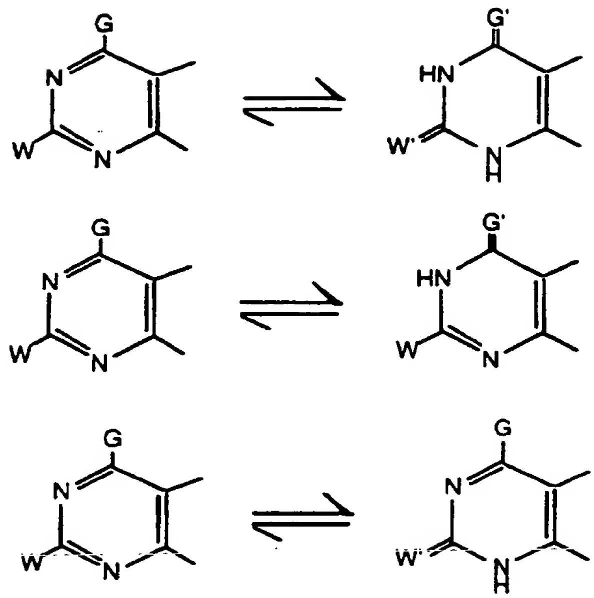
It is understood that protecting groups are chosen to perform their "protecting" function and are also chosen to be removable from the substrate group without the cleavage reaction affecting the remainder of the substrate group.

The compounds of this invention are herein described as embodying both the pyrrolo[2,3-d]pyrimidine heterocyclic ring system which ring system is numbered as follows:



and the 5,6-dihydropyrrolo[2,3-d]pyrimidine heterocyclic ring system, which is numbered in a similar manner.

In the above formulae, the compounds of this invention can exist as an equilibrium mixture with their tautomeric isomers. Illustrated below are the partial structural formulae capable of undergoing tautomerism, with the equilibria among them being shown as well.



where G,W = NH_2, OH, or SH;
G',W' = NH, O or S.

Throughout this specification, for the purpose of convenience of expression, the amino, hydroxyl and mercapto forms are to be described, with the corresponding designations being adopted. However, in any description, their tautomers, i.e. the imino, oxo and thioxo forms are understood to be included in the scope of this invention.

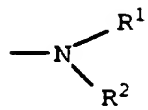
With all of these tautomers, it is the oxo, amino, and mercapto structures that dominate. Note that the dihydro pyrrolo[2,3-d]pyrimidine structure has no G substituent, rather the substituent at the 4-position on the dihydro pyrrolo[2,3-d]pyrimidine structure is H.

A preferred group for G is -OH, with the understanding that the structure exists primarily in the G' keto form.

Preferred groups for W are $-NH_2$ and $-CH_3$.

A preferred group for L is optionally substituted $-CH_2CH_2-$.

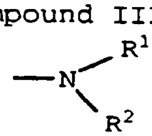
Preferred groups for B are optionally substituted 1,4-phenylene and 2,5-thiophenediyl.

Preferred groups for  are as follows:

-alanine,
-arginine,
-asparagine,
-aspartic acid,
-cysteine,
-cystine,
-glutamine,
-glycine,
-histidine,
-hydroxyproline,
-isoleucine,
-leucine,
-lysine,
-methionine,
-phenylalanine,
-proline,
-serine,
-threonine,
-tryptophan,
-tyrosine,
-valine,
-o-chlorophenylalanine,
-m-chlorophenylalanine,
-p-chlorophenylalanine,
-N'-methanesulfonyl glutamine,
-N'-triphenylmethyl glutamine,
-phenylglycine,
-thien-2-ylglycine,
-o-carboxyphenylglycine,
-m-carboxyphenylglycine,
-p-carboxyphenylglycine,

-o-hydroxyphenylglycine,
-m-hydroxyphenylglycine,
-p-hydroxyphenylglycine,
-cyclohexylglycine,
-2'-carboxycyclohexylglycine,
-3'-carboxycyclohexylglycine.
-4'-carboxycyclohexylglycine,
-o-nitrophenylglycine,
-m-nitrophenylglycine,
-p-nitrophenylglycine,
-o-aminophenylglycine,
-m-aminophenylglycine,
-p-aminophenylglycine,
-o-chlorophenylglycine,
-m-chlorophenylglycine,
-p-chlorophenylglycine,
-o-bromophenylglycine,
-m-bromophenylglycine,
-p-bromophenylglycine,
-o-iodophenylglycine,
-m-iodophenylglycine,
-p-iodophenylglycine,
-o-fluorophenylglycine,
-m-fluorophenylglycine,
-p-fluorophenylglycine,
-2-amino-adipic acid,
-2-amino-butanoic acid,
-2-amino-3-hydroxybutanoic acid,
-2-amino-4-phenylbutanoic acid,
-2-amino-1,4-butanedioic acid,
-3,3-dimethyl-2-amino butanoic acid,
-2-amino-3-methyl-1,5-pentanedioic acid,
-3-methyl-2-amino-pentanoic acid,
-2-amino-pentanoic acid,
-2-amino-1,7-heptanedioic acid,
-3-carboxy-3-aminopropanesulfonic acid,
-N-[1-carboxy-3-(tetrazol-5-yl)propyl]amino,

-N-[1-carboxy-7-(tetrazol-5-yl)heptyl]amino,
-N-[1-carboxy-4-aminobutyl]amino,
-N-[1-carboxy-4-(tert-butoxycarbonyl amino)butyl]amino,
-N-[1-carboxy-4-(phthalimido-1-yl)butyl]amino,
-N-{[1-carboxy-4-(N'-o-carboxybenzoyl)amino]butyl}amino,
-N-[1-carboxy(3-methoxycarbonyl)propyl]amino,
-N-{2-[tetrazol-5-yl]ethyl}amino,
-N-{3-[tetrazol-5-yl]propyl}amino,
-N-{4-[tetrazol-5-yl]butyl}amino,
-N-{5-[tetrazol-5-yl]pentyl}amino,
-N-{6-[tetrazol-5-yl]hexyl}amino,
-N-{7-[tetrazol-5-yl]heptyl}amino,
-2-carboxypiperidine,
-3-carboxypiperidine,
-4-carboxypiperidine, and
-methionine sulfoxide.

As stated previously, for α-amino acid residue preferred groups the amino acid residue group is bonded to the carbonyl group of Compound III through the α-amino nitrogen. For other preferred  groups, the group is bonded to the carbonyl group of Compound III through the preferred groups terminal nitrogen.

The following are preferred compounds of formula (III).

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}alanine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}arginine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}asparagine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}aspartic acid,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}cysteine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}cystine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}glycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}histidine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}hydroxyproline,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}isoleucine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}leucine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}lysine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}methionine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}phenylalanine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}proline,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}serine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}threonine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}tryptophan,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}tyrosine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}valine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}alanine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}arginine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}asparagine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}aspartic acid,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}cysteine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}cystine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}glycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}histidine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}hydroxyproline,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}isoleucine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}leucine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}lysine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}methionine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}phenylalanine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}proline,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}serine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}threonine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}tryptophan,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}tyrosine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl)valine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}alanine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}arginine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}asparagine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}aspartic acid,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}cysteine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}cystine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}glycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}histidine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}hydroxyproline,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}isoleucine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}leucine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}lysine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}methionine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}phenylalanine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}proline,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}serine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}threonine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}tryptophan,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}tyrosine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}valine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}alanine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}arginine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}asparagine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}aspartic acid,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}cysteine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}cystine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}glycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}histidine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}hydroxyproline,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}isoleucine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}leucine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}lysine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}methionine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}phenylalanine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}proline,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}serine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}threonine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}tryptophan,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}tyrosine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}valine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}alanine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}arginine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}asparagine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}aspartic acid,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}cysteine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}cystine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}glycine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}histidine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}hydroxyproline,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}isoleucine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}leucine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}lysine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}methionine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}phenylalanine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}proline,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}serine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}threonine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}tryptophan,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}tyrosine,

N-{[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}valine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}alanine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}arginine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}asparagine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}aspartic acid,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}cysteine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}cystine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}glycine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}histidine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}hydroxyproline,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}isoleucine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}leucine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}lysine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}methionine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}phenylalanine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}proline,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}serine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}threonine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}tryptophan,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}tyrosine,

N-{[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}valine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}alanine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}arginine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}asparagine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}aspartic acid,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}cysteine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}cystine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}glycine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}histidine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}hydroxyproline,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}isoleucine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}leucine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}lysine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}methionine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}phenylalanine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}proline,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}serine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}threonine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}tryptophan,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}tyrosine,

N-{2-[(2-methyl-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}valine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}alanine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}arginine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}asparagine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}aspartic acid,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}cysteine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}cystine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}glycine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}histidine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}hydroxyproline,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}isoleucine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}leucine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}lysine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}methionine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}phenylalanine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}proline,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}serine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}threonine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}tryptophan,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}tyrosine,

N-{2-[(2-amino-5,6-dihydropyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}valine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-aminoadipic acid,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-aminoadipic acid,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-aminoadipic acid,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-aminoadipic acid,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-amino-1,7-heptanedioic acid,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-amino-1,7-heptanedioic acid,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-amino-1,7-heptanedioic acid,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-amino-1,7-heptanedioic acid,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-amino-3-methyl-1,5-pentanedioic acid,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-amino-3-methyl-1,5-pentanedioic acid,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-amino-3-methyl-1,5-pentanedioic acid,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-amino-3-methyl-1,5-pentanedioic acid,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-amino-3-methyl-1,4-butanedioic acid,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-amino-3-methyl-1,4-butanedioic acid,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-amino-3-methyl-1,4-butanedioic acid,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-amino-3-methyl-1,4-butanedioic acid,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-3-(tetrazol-5-yl)propyl]amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-3-(tetrazol-5-yl)propyl]amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-3-(tetrazol-5-yl)propyl]amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-3-(tetrazol-5-yl)propyl]amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-7-(tetrazol-5-yl)heptyl]amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-7-(tetrazol-5-yl)heptyl]amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-7-(tetrazol-5-yl)heptyl]amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-7-(tetrazol-5-yl)heptyl]amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-4-aminobutyl]amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-4-aminobutyl]amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-4-aminobutyl]amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-4-aminobutyl]amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-4-(<u>tert</u>-butoxycarbonylamino)butyl]amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-4-(<u>tert</u>-butoxycarbonylamino)butyl]amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-4-(tert-butoxycarbonylamino)butyl]amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-4-(tert-butoxycarbonylamino)butyl]amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-4-(phthalimido-1-yl)butyl]amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-4-(phthalimido-1-yl)butyl]amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-4-(phthalimido-1-yl)butyl]amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-4-(phthalimido-1-yl)butyl]amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-{[1-carboxy-4-(N'-o-carboxybenzoyl)amino]butyl}amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-{[1-carboxy-4-(N'-o-carboxybenzoyl)amino]butyl}amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-{[1-carboxy-4-(N'-o-carboxybenzoyl)amino]butyl}amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-{[1-carboxy-4-(N'-o-carboxybenzoyl)amino}butyl}amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-(3-methoxycarbonyl)propyl]amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-(3-methoxycarbonyl)propyl]amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-(3-methoxycarbonyl)propyl]amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-(3-methoxycarbonyl)propyl]amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-(3-benzyloxycarbonyl)propyl]amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-[1-carboxy-(3-benzyloxycarbonyl)propyl]amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-(3-benzyloxycarbonyl)propyl]amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-[1-carboxy-(3-benzyloxycarbonyl)propyl]amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N'-methanesulfonylglutamine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N'-methanesulfonylglutamine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N'-methanesulfonylglutamine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N'-methanesulfonylglutamine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N'-triphenylmethylglutamine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N'-triphenylmethylglutamine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N'-triphenylmethylglutamine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N'-triphenylmethylglutamine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-3-methyl-2-aminopentanoic acid,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-3-methyl-2-aminopentanoic acid,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-3-methyl-2-aminopentanoic acid,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-3-methyl-2-aminopentanoic acid,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-3,3-dimethyl-2-aminobutanoic acid,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-3,3-dimethyl-2-aminobutanoic acid,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-3,3-dimethyl-2-aminobutanoic acid,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-3,3-dimethyl-2-aminobutanoic acid,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}phenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}phenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}phenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}phenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-fluorophenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-fluorophenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-fluorophenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-fluorophenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}thien-2-ylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}thien-2-ylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}thien-2-ylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}thien-2-ylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-carboxyphenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-carboxyphenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-carboxyphenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-carboxyphenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-m-carboxyphenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-m-carboxyphenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-m-carboxyphenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-m-carboxyphenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-p-carboxyphenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-p-carboxyphenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-p-carboxyphenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-p-carboxyphenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-hydroxyglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-hydroxyglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-hydroxyglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-hydroxyglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-m-hydroxyglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-m-hydroxyglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-m-hydroxyglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-m-hydroxyglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-p-carboxycyclohexylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-p-carboxycyclohexylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-p-hydroxyglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-p-hydroxyglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2'-carboxycyclohexylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2'-carboxycyclohexylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2'-carboxycyclohexylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2'-carboxycyclohexylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}cyclohexylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}cyclohexylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}cyclohexylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}cyclohexylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-chlorophenylalanine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-chlorophenylalanine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-chlorophenylalanine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-chlorophenylalanine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-(2-[tetrazol-5-yl]ethyl)amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-(2-[tetrazol-5-yl]ethyl)amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-(2-[tetrazol-5-yl]ethyl)amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-(2-[tetrazol-5-yl]ethyl)amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-(3-[tetrazol-5-yl]propyl)amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-(3-[tetrazol-5-yl]propyl)amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-(3-[tetrazol-5-yl]propyl)amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-(3-[tetrazol-5-yl]propyl)amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-(4-[tetrazol-5-yl]butyl)amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-(4-[tetrazol-5-yl]butyl)amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-(4-[tetrazol-5-yl]butyl)amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-(4-[tetrazol-5-yl]butyl)amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-(5-[tetrazol-5-yl]pentyl)amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-(5-[tetrazol-5-yl]pentyl)amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-(5-[tetrazol-5-yl]pentyl)amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-(5-[tetrazol-5-yl]pentyl)amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-(6-[tetrazol-5-yl]hexyl)amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-(6-[tetrazol-5-yl]hexyl)amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-(6-[tetrazol-5-yl]hexyl)amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-(6-[tetrazol-5-yl]hexyl)amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-(7-[tetrazol-5-yl]heptyl)amine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-N-(7-[tetrazol-5-yl]heptyl)amine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-(7-[tetrazol-5-yl]heptyl)amine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-N-(7-[tetrazol-5-yl]heptyl)amine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-carboxypiperidine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-carboxypiperidine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-carboxypiperidine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-carboxypiperidine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-3-carboxypiperidine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-3-carboxypiperidine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-3-carboxypiperidine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-3-carboxypiperidine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-4-carboxypiperidine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-4-carboxypiperidine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-4-carboxypiperidine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-4-carboxypiperidine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-aminopentanoic acid,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-aminopentanoic acid,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-aminopentanoic acid,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-aminopentanoic acid,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-aminobutanoic acid,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-aminobutanoic acid,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-aminobutanoic acid,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-aminobutanoic acid,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-amino-3-hydroxybutanoic acid,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-amino-3-hydroxybutanoic acid,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-amino-3-hydroxybutanoic acid,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-amino-3-hydroxybutanoic acid,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-amino-4-phenylbutanoic acid,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-2-amino-4-phenylbutanoic acid,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-amino-4-phenylbutanoic acid,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-2-amino-4-phenylbutanoic acid,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-3-carboxy-3-aminopropanesulfonic acid,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-3-carboxy-3-aminopropanesulfonic acid,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-3-carboxy-3-aminopropanesulfonic acid,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-3-carboxy-3-aminopropanesulfonic acid,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}methionine sulfoxide,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}methionine sulfoxide,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}methionine sulfoxide,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}methionine sulfoxide,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-nitrophenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-nitrophenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-nitrophenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-nitrophenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-m-nitrophenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-m-nitrophenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-m-nitrophenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-m-nitrophenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-p-nitrophenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-p-nitrophenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-p-nitrophenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-p-nitrophenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-aminophenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-aminophenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-aminophenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-aminophenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-m-aminophenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-m-aminophenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-m-aminophenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-m-aminophenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-p-aminophenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-p-aminophenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-p-aminophenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-p-aminophenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-chlorophenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-o-chlorophenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-chlorophenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-o-chlorophenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-m-chlorophenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-m-chlorophenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-m-chlorophenylglycine,

N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-m-chlorophenylglycine,

N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-p-chlorophenylglycine,

N-{[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}-p-chlorophenylglycine,

N-{2-[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-p-chlorophenylglycine, and

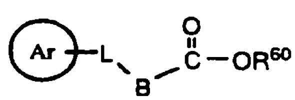
N-{2-[(2-amino-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-ylcarbonyl}-p-chlorophenylglycine, and

the pharmaceutically acceptable salts and solvates thereof.

For each of the above-identified compounds, all tautomeric equivalents of each structure are intended to be included. For example N-{[(2-methyl-4-hydroxypyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}alanine is equivalent to N-{[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]phen-4-ylcarbonyl}alanine.

The compounds of the present invention can be made via a process entitled "Rapid Analogue Process" or RAP. The "rapid" part of the process refers to the relative rapid rate that non-classical antifolates can be synthesized, isolated and purified, when using this process.

The process to make a compound of formula (III) involves reacting an "active ester" of formula (I):



(I)

where , L and B are as defined previously, R^{60} is selected from the group consisting of N-hydroxysuccinimidyl, N-hydroxysulphosuccinimidyl and salts thereof, 2-nitrophenyl, 4-nitrophenyl and 2,4-dichlorophenyl, with an amine of formula (II):

$$HNR^1R^2 \qquad (II)$$

where R^1 and R^2 are as defined previously, in the presence of a silylating agent.

Silylating agents are selected from any reagent capable of attaching a silyl group to a target group. Typical silylating agents include any reagent with a trialkylsilyl group such as trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, and t-butyldimethylsilyl, any reagent with an alkylarylsilyl group such as tribenzylsilyl, diphenylmethylsilyl, t-butylmethoxyphenylsilyl and tri-p-xylylsilyl, and any reagent with a triarylsilyl group such as triphenylsilyl. The preferred silylating agent is a trimethyl silylating agent. Typical trimethyl silylating agents include N,O-Bis(trimethylsilyl) acetamide, allyltrimethylsilane, N,O-Bis(trimethylsilyl)-carbamate, N,N-Bis(trimethylsilyl)methylamine, Bis(trimethylsilyl)sulfate, N,O-Bis(trimethylsilyl)trifluoroacetamide, N,N-Bis(trimethylsilyl)urea, trimethylsilane, ethyl trimethyl silylacetate, hexamethyldisilane, hexamethyldisilazane, hexamethyldisiloxane, hexamethyldisilylthiane, (isopropenyloxy)trimethyl silane, 1-methoxy-2-methyl-1-trimethyl-siloxy-propene, (methylthio)trimethylsilane, methyl 3-trimethylsiloxy-2-butenoate, N-methyl-N-trimethylsilylacetamide, methyl trimethylsilylacetate, N-methyl-N-trimethylsilylhepta-fluorobutyramide, N-methyl-N-trimethylsilyl-trifluoroacetamide, (phenylthio)trimethylsilane, trimethylbromosilane, trimethylchlorosilane, trimethyliodosilane, 4-trimethylsiloxy-3-penten-2-one, N-(trimethylsilyl)acetamide, trimethylsilyl acetate, trimethylsilyl azide, trimethylsilyl benzenesulfonate, trimethylsilyl cyanide, N-trimethylsilyldiethylamine, N-trimethylsilyldimethylamine, trimethylsilyl N,N-dimethylcarbamate, 1-

(trimethylsilyl)imidazole, trimethylsilyl methanesulfonate, 4-(trimethylsilyl)morpholine, 3-trimethylsilyl-2-oxazolidinone, trimethylsilyl trichloroacetate, trimethylsilyl trifluoroacetate and trimethylsilyl trifluoromethane sulfonate.

A more preferred silylating agent is N,O-bis-(trimethylsilyl) acetamide. The N,O-Bis (trimethylsilyl)acetamide acts to protect carboxylic acid groups present, as well as any hydroxy group present, on the active ester and/or the amine of formula II.

An added benefit of using a trimethylsilyl protecting agent is that the trimethylsilyl protected forms of the amine/active ester tend to be more soluble which leads to better yields in the reaction. It is also believed, without intending to be bound thereby, that the silylation of the N atoms activates the amino group towards nucleophilic attack. Protection of the carboxylic acid groups on the active ester of formula (I) and the amine of formula (II) permits the coupling of the active ester and amine to form the compounds of formula (III).

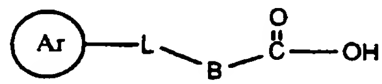
The reaction takes place at a temperature preferably between about 25° C and about 100° C, more preferably between about 40° C and about 80° C, and most more preferably between about 50° C and about 60° C.

The reaction should take place in a solvent. Any non-reactive organic solvent such as dimethylformamide, ethyl acetate, methylene chloride, toluene or acetonitrile is suitable. The preferred solvent is dimethylformamide.

It takes between about 5 hours and 70 hours to make a measurable amount of product. Preferably the reaction is run for about 10 hours to about 60 hours and more preferably the reaction is run for about 16 hours to about 48 hours.

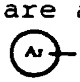
In order to maximize the number of compounds made typically one compound of formula (I) is made and then reacted with different compounds of formula (II) to form the

antifolate compounds of formula (III). Compounds of formula I can be made by reacting an acid of formula (IV):

 (IV)

where , L and B are as defined previously, with an alcohol under known conditions. For example when the active ester is a N-hydroxysuccinimide (NHS) ester, a compound of formula (IV) is reacted with N-hydroxysuccinimide (NHS) in a suitable solvent, such as dimethylformamide (DMF), under known conditions (such as room temperature stirring for approximately 24 hours after addition of 1,3-dicyclohexylcarbodimide). The preferred active ester is a N-hydroxysuccinimide ester.

Compounds of formula (IV) can be made using known technology in the art of pyrrolo[2,3-d]pyrimidinyl fused ring system antifolate chemistry. See, for example, U.S. Patent No. 5,106,974 to Akimoto et al., U.S. Patent No. 4,997,838 to Akimoto et al., U.S. Patent No. 4,818,819 to Taylor et al., U.S. Patent No. 5,028,608 to Taylor et al., U.S. Patent No. 5,344,932 to Taylor et al., U.S. Patent No. 5,254,687 to Taylor et al., U.S. Patent No. 5,416,211 to Barnett et al., U.S. Patent No. 5,403,843 to Skimoto et al., and Synthesis and Antitumor Activity of Pyrrolo[2,3-d] Pyrimidine Antifolates with a Bridge Chain Containing a Nitrogen Atom, Aso et al., Chem. Phar. Bull., 43(2) 256-261(1995) which are all incorporated by reference.

Where  is the 5,6-dihydropyrrolo[2,3-d]pyrimidin-yl fused ring system, compounds of formula (IV) can be made by following the procedures described in, "The Synthesis of N-{2-Amino-4-Substituted[(Pyrrolo[2,3-d]Pyrimidin-5-yl)Ethyl]Benzoyl}-L-Glutamic Acids as Antineoplastic Agents", Shih and Gossett, Heterocycles, Vol. 35, No. 2, 1993.

Amines of formula (II) can be made by standard techniques known in the art. See for example, Organic Chemistry, pp. 828-843 by Morrison & Boyd, 6th Edition, 1992 by Prentice-Hall, Inc., and Advanced Organic Chemistry, by J. March, 4th Edition, 1992 by John Wiley and Sons, Inc. or they can be obtained through standard reagent supply companies such as Sigma Chemical Company, P.O. Box 14508, St. Louis, MO 63178.

The reaction of compound (I) and compound (II) to make the compound of formula (III) can also take place in the presence of a suitable strong base. Such suitable strong bases include NaOH, KOH, etc. The preferred strong base is NaOH.

After the antifolate compounds of formula (III) are synthesized, they must be worked-up to provide an antifolate compound suitable for testing or use. An advantage of the claimed process is that it includes a rapid work-up procedure wherein the compound of formula (III) is isolated from the reaction mixture by performing the following steps:

a) optionally adding a suitable diamine;
b) adding a suitable aqueous acid;
c) separating the product from its solvent;
d) preparing the product physically for collecting, washing and drying; and
e) collecting, washing and drying the product.

A suitable diamine is any diamine capable of reacting with unreacted active ester to create a product with an amine functionality. This product with an amine functionality can then be washed out of the reaction mixture, along with unreacted HNR^1R^2. One such suitable diamine is ethylene diamine. The addition of the diamine is optional, though preferred.

The suitable acid is a mineral acid selected from the group consisting of HCl, HBr, HI, and HF. The preferred suitable acid is HCl. The most preferred suitable acid is 1 Normal aqueous HCl.

Separating the product from its solvent can be done by any technique known in the art. One such method is to strip the solvent from the product by heating the solvent. When the solvent is a high-boiling solvent another solvent, or mixture of solvents, can be added to form a lower-boiling azeotropic mixture which can be boiled off at a lower temperature. Typical solvents used to create a lower boiling azeotropic solvent mixture can be selected from the group consisting of o-xylene, m-xylene, p-xylene, toluene, benzene, and mixtures thereof. The most preferred solvent for this purpose is a mixture of o-xylene, m-xylene and p-xylene.

Preparing the product physically for collecting, washing and drying involves breaking up the clumped product into particles sufficiently small so that the particles may readily be collected by any suitable technique such as by filtration or evaporation. After collection, the product is washed and dried. Any method can be used to break up the product. A preferred method is sonicating the product in the presence of acid.

Collecting, washing, and drying can be accomplished using standard techniques in the art of organic chemistry. For example, the product can be collected by filtering it through a Buchner funnel, then washing it with water and then ether, and then drying it in a vacuum oven.

By following this non-conventional workup and purification procedure the time involved is reduced significantly because there is no need for traditional time consuming separation techniques such as chromatography.

This invention includes pharmaceutically acceptable salts and solvates of all compounds. The pharmaceutically acceptable salts of the invention are typically formed by reacting a compound of formula (III) which possesses one or more suitable acidic or basic functionalities with an equimolar or slight excess amount of base or acid. The reactants generally are combined in a mutual solvent such as diethyl ether or benzene for acid

addition salts, or water or alcohols for base addition salts. The salt usually precipitates out of solution within about 1 hour to about 10 days, and can be isolated by filtration or other conventional means.

In addition, some of the compounds of the present invention may form solvates with water or common organic solvents. Such solvates are included as compounds of this invention.

It is also contemplated that the acid portions of these compounds may be modified to form esters, using techniques known in the art. These ester compounds typically contain C_1-C_4 alkyl moieties in place of the acid hydrogen. These ester intermediates are also considered to be part of the invention.

The compounds of the present invention may be administered to any mammal. Of all mammals, it is believed that humans will benefit the most from administration of these compounds.

The compounds of the present invention are antineoplastic agents. An embodiment of the present invention provides a method of treating susceptible neoplasms in mammals, preferably humans, in need of such treatment. The present compounds are useful in inhibiting the growth of neoplasms or "cancers", including, but not limited to, carcinoma, sarcoma, melanoma, colorectal, choriocarcinoma, prostate, leukemia, breast, squamous or small cell lung cancer, non-small cell lung cancer, ovarian, testicular, adenocarcinoma, epidermal, lymphosarcoma, pancreatic, head and neck, kidney, bone and liver cancer.

The compounds are tested for their ability to inhibit the growth of certain tumor cell lines and data reported as standard IC_{50}'s and Ki inhibition constants.

The compounds of the present invention are also useful in the treatment of psoriasis and arthritis, in mammals, preferably humans.

The compounds of the present invention can be administered orally, parenterally, or by means of

insufflation or by insertion of a suppository. The compounds can be administered individually or in combination, preferably parenterally, and usually in the form of a pharmaceutical composition. Parenteral routes of administration include intramuscular, intrathecal, subcutaneous, intravenous, intra-arterial, intraorbital, intracapsular, intraspinal, and intrasternal. Oral dosage forms, including tablets and capsules, contain from 1 to 3000 mg of drug per unit dosage. Isotonic saline solutions containing 1-100 mg/mL can be used for parenteral administration.

Compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Accordingly, the present invention also includes pharmaceutical compositions comprising as active ingredient one or more compounds of formula (III) associated with at least one pharmaceutically acceptable carrier, diluent or excipient.

In making the compositions of the present invention, as well as compositions containing one or more other compounds of formula (III), the active ingredients are usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum arabic, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidinone, cellulose, water, syrup, and methyl cellulose, the formulations can additionally include lubricating agents such as talc, magnesium stearate and

mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and propyl-hydroxybenzoates, sweetening agents or flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form with each dosage normally containing from about 0.1 milligrams per square meter of body surface area (mg/M^2) to about 3000 mg/M^2, more usually about 10 mg/M^2 to about 250 mg/M^2 of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient.

However, it will be understood that the amount of the compound actually administered, and the frequency of administration, will be determined by a physician or veterinarian in light of the relevant circumstances including the relative severity of a disease state, the choice of compound to be administered, the age, weight, and response of the individual patient, and the chosen route of administration. Therefore, the above dosage ranges are not intended to limit the scope of this invention in any way.

EXAMPLES

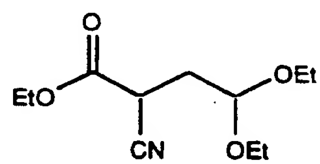
The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

The terms "NMR", "IR", "UV" or "MS" following a synthesis protocol indicates that the nuclear magnetic

resonance spectrum, infrared spectrum, ultraviolet spectrum or mass spectrometry, respectively, were performed and the data were consistent with the title product. All other terms and abbreviations used in the instant examples have their normal meanings unless otherwise designated. For example "°C" refers to degrees Celsius; "DMF" refers to dimethylformamide, "g" refers to gram or grams; "h" refers to hour or hours; "kPa" refers to kiloPascals; "L" refers to liter or liters; "mg" refers to milligrams; "ml" refer to milliliter or milliliters; "mol" refers to moles,; "mmol" refers to millimole or millimoles; "N" refers to normal or normality; "psi" refers to pounds per square inch; and "RT" refers to room temperature.

Preparation 1

Step 1: Synthesis of ethyl 4,4-diethoxy-2-cyano-butanoate

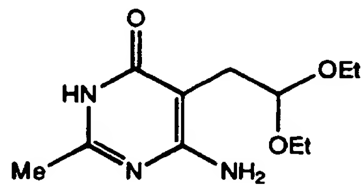


A stirred mixture of ethyl cyanoacetate (550 mL, 5.17 mol), bromo diethylacetal (155 mL, 1.03 mol), powdered potassium carbonate (140 g, 1.01 mol), and sodium iodide (20.1 g, 0.13 mol) was heated at 130°C for 4 hours. The mixture was cooled to room temperature, diluted with water (1.2 L) and then extracted with diethyl ether (4 x 1 L). The combined organics were washed with brine (3 x 250 mL), dried ($MgSO_4$), and then concentrated to give a brown oil which was distilled under reduced pressure to give the product as a clear oil (99.10 g, 42%).

b.p. (0.03 torr): 71-80°C; ^1H NMR ($CDCl_3$) δ 4.70 (t, J = 5.70 Hz, CH), 4.27 (q, J = 7.17 Hz, CH_2), 3.77 - 3.64 (m, CH, CH_2), 3.59 - 3.50 (m, CH_2), 2.34 - 2.15 (m,

CH_2), 1.33 (t, J = 7.17 Hz, CH_3), 1.23 (t, J = 6.99 Hz, CH_3), 1.21 (t, J = 6.99 Hz, CH_3) ppm; IR (neat) υ 3528, 3020, 2982, 2932, 2900, 2253, 1746, 1263, 1127, 1060 cm^{-1}; MS (FI) 230 ($[MH]^+$, 15).

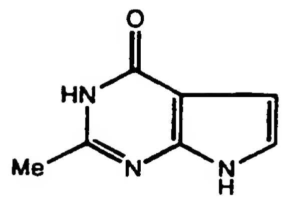
Step 2: Synthesis of 2-methyl-3H-4-oxo-5-(2,2-diethoxy-ethyl)-6-amino-pyrimidine



Sodium metal (8.10 g, 352 mmol) was added to dry distilled methanol (100 mL) and stirred for 0.5 hours. Methyl acetamidine (11.13 g, 117 mmol) was added and the resulting mixture was refluxed for 0.5 hours and then cooled to room temperature. Neat cyanoester from Step 1 (26.83 g, 117 mmol) was then added and the resulting mixture was refluxed for 1.5 hours. The solvent was removed in vacuo and the resulting residue diluted with water (100 mL) and the pH adjusted to 6 with conc. HCl producing a precipitate which was filtered and dried to give the pyrimidine as a white solid (19.15 g, 68%).

^1H NMR (DMSO-d_6) δ 11.42 (s, NH), 5.99 (s, NH_2), 4.54 (t, J = 5.52 Hz, CH), 3.65-3.55 (m, CH_2), 3.45-3.35 (m, CH_2), 3.34 - 3.32 (hidden m, CH_2), 2.11 (s, CH_3), 1.07 (t, J = 6.99 Hz, 6 H, 2 CH_3) ppm; IR (KBr) υ 3465, 3314, 3166, 2973, 2928, 2855, 1635, 1606, 1455, 1287, 1062, 809 cm^{-1}; MS (FD) 241 (M^+, 100).

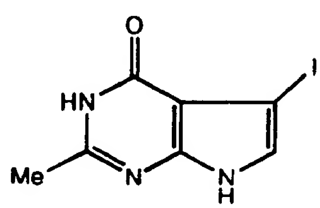
Step 3: Synthesis of 2-methyl-3H-4-oxo-pyrrolo[2,3-d]-pyrimidine



A suspension of the pyrimidine diethylacetal from Step 2 (19 g, 78.80 mmol) in 1N aqueous HCl (210 mL) was stirred at room temperature for 4 hours. The reaction mixture was filtered and the solid washed with water (1 L), diethyl ether (1 L), and then dried to give the pyrrolopyrimidine as a white solid (11.70 g, 99%).

^1H NMR (DMSO-d_6) δ 11.67 (s, NH), 11.62 (s, NH), 6.94 (dd, J = 2.57 and 3.31 Hz, Pyr H), 6.37 (dd, J = 2.21 and 3.31 Hz, Pyr H), 2.30 (s, CH_3) ppm; IR (KBr) υ 3404, 3170, 3102, 2932, 2847, 1657, 1602, 1370, 1297, 1190, 901, 809 cm^{-1}; UV (EtOH) λ_{max} 213 (ε = 14863), 261 (ε = 9888) nm; MS (FD) 149 (M^+, 100); Anal. calcd. for $C_7H_7N_3O$ requires: C, 56.37; H, 4.73; N, 28.17% ; Found: C, 56.09; H, 4.62; N, 27.92%.

<u>Step 4</u>: Synthesis of 2-methyl-3H-4-oxo-5-iodo-pyrrolo[2,3-d]pyrimidine

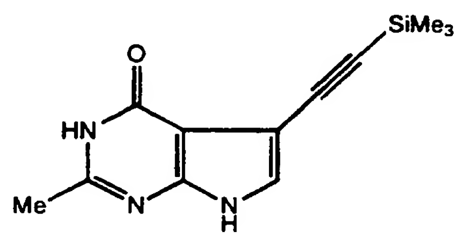


A stirred solution of 2-methyl-3H-4-oxo-pyrrolo-[2,3-d]pyrimidine (250 mg, 1.68 mmol), and N,O-bis(trimethylsilyl)acetamide (3.8 mL, 15.4 mmol), in DMF (5 mL) was heated at 40°C under nitrogen for 2 hours. The mixture was then cooled to -8°C in an ice/brine bath and N-iodo-succinimide (1.55 g, 6.88 mmol) was added. The

reaction mixture was stirred for 0.75 hours then quenched with water (5 mL) to produce a precipitate which was filtered, washed with water and dried to provide the iodide as a light yellow solid (1.77 g, 96%).

^{1}H NMR (DMSO-d_6) δ 11.96 (s, NH), 11.77 (s, NH), 7.13 (d, J = 2.21 Hz, Pyr H), 2.28 (s, CH_3) ppm; IR (KBr) υ 3160, 3063, 2920, 2823, 1666, 1601 cm^{-1}; UV (EtOH) λ_{max} 224 (ε = 13228), 272 (ε = 9086) nm; MS (FD) 275 (M^+, 100); Anal. calcd. for $C_7H_6N_3IO$ requires: C, 30.57; H, 2.20; N, 15.27% ; Found: C, 30.56; H, 2.26; N, 15.02%.

Step 5: Synthesis of 2-methyl-3H-4-oxo-5-(trimethylsilylethyne)-pyrrolo[2,3-d]pyrimidine

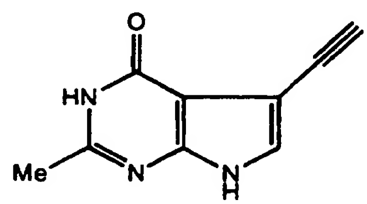


A stirred solution of the iodide from Step 4 (21 g, 76.4 mmol), and N,O-bis(trimethyl)acetamide (42 mL, 170.3 mmol), in DMF (120 mL) was heated at 40°C under nitrogen for 2 hours The reaction solution was allowed to cool to room temperature and then trimethylsilylacetylene (16.2 mL, 114.5 mmol), copper (II) iodide (1.45 g, 7.6 mmol) and triethylamine (11.7 mL, 84.1 mmol) added followed by a preformed catalyst mixture of palladium chloride (1.35 g, 7.6 mmol), and triphenyl phosphine (4.0 g, 15.4 mmol) in DMF (11 mL). The resulting mixture was stirred at room temperature for 18 hours,diluted with acetonitrile (510 mL) and the reaction mixture filtered through a sintered glass funnel. To the rapidly stirring filtrate was added water (15 mL) dropwise causing a solid to precipitate which was

filtered, rinsed with fresh acetonitrile (500 mL) and dried to give the product as a light green solid (13.7 g, 73%).

^{1}H NMR (DMSO-d_6) δ 11.76 (s, NH), 11.56 (s, NH), 7.12 (d, J = 2.57 Hz, Pyr H), 2.09 (s, CH_3), 0.00 (s, 9 H $SiMe_3$) ppm; IR (KBr) υ 3098, 2960, 2918, 2814, 2163, 1662, 1605, 1302, 1249, 1074, 863, 842 cm^{-1}; UV (EtOH) λ_{max} 235 (ε = 14898), 242 (ε = 14782), 277 (ε = 13534) nm; MS (FD) 245 (M^+, 100); Anal. calcd. for $C_{12}H_{15}N_3O$ requires: C, 58.74; H, 6.16; N, 17.13% ; Found: C, 58.46; H, 5.96; N, 17.12%.

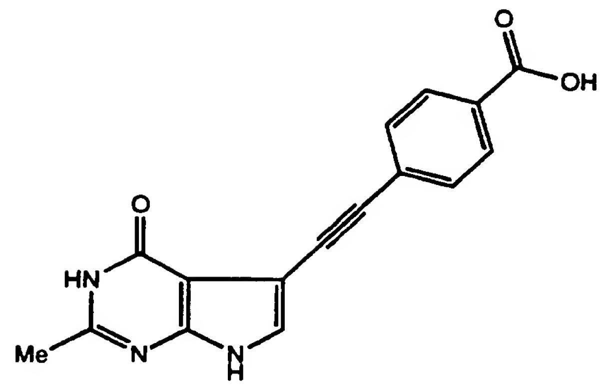
<u>Step 6</u>. Synthesis of 2-methyl-3H-4-oxo-5-ethynepyrrolo-[2,3-d]pyrimidine



To a stirred solution of the TMS-pyrrolopyrimidine of Step 5 (11.0 g, 44.9 mmol) in dry DMF (150 mL) was added tetra-n-butylammonium fluoride (12.3 g, 47.2 mmol) at room temperature. The mixture was stirred at room temperature for 4 hours and then glacial acetic acid (3.4 mL) was added followed by water (200 mL) causing a solid to precipitate which was filtered, washed with water (500 mL) and dried to give the acetylene as a tan solid (5.7 g, 73%).

^{1}H NMR (DMSO-d_6) δ 11.95 (s, NH), 11.83 (s, NH), 7.30 (d, J = 2.57 Hz, Pyr H), 3.88 (s, CH), 2.29 (s, CH_3) ppm; IR (KBr) υ 3248, 3170, 3093, 2920, 2838, 1656, 1604, 1448, 1294, 1141, 814, 792 cm^{-1}; UV (EtOH) λ_{max} 230 (ε = 14648), 271 (ε = 10960) nm; MS (FD) 173 (M^+, 100).

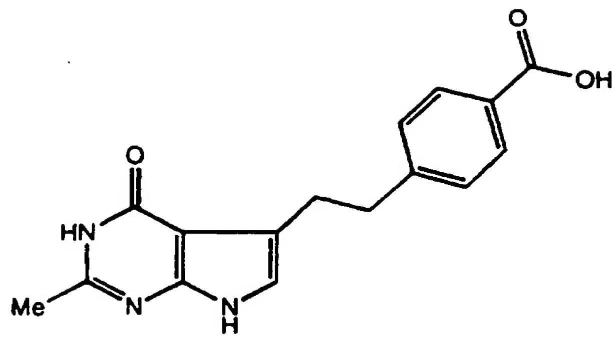
<u>Step 7</u>: Synthesis of 2-methyl-3H-4-oxo-5-(2-(4-carboxyphenyl)ethynyl)pyrrolo[2,3-d]pyrimidine



A stirred mixture of pyrrolopyrimidine of Step 6(2.26 g, 13.0 mmol), p-iodobenzoic acid (3.24 g, 13.0 mmol), and N,O-bis(trimethylsilyl)acetamide (11 mL, 44.6 mmol) in dry acetonitrile (65 mL) was heated at 40°C under nitrogen for 4 hours. Triethylamine (3.4 mL, 24.4 mmol) was added and the mixture was deoxygenated with dry nitrogen for 20 minutes. A preformed catalyst mixture containing palladium chloride (119 mg, 0.67 mmol) and triphenylphosphine (347 mg, 1.32 mmol) in acetonitrile (10 mL) was added and the resulting mixture was heated at reflux for 3 hours The reaction mixture was cooled to 0°C and water (1.8 mL) added dropwise causing a solid to precipitate which was filtered, rinsed with acetonitrile and dried to give the coupled product as a gray solid (3.15 g, 82%).

^{1}H NMR (DMSO-d_6) δ 13.03 (broad singlet, COOH), 12.12 (broad singlet, NH), 11.89 (bs, NH), 7.96 (d, J = 8.46 Hz, ArH_2), 7.58 (d, J = 8.09 Hz, ArH_2), 7.46 (d, J = 2.57 Hz, Pyr H), 2.32 (s, CH_3) ppm; IR (KBr) υ 2918, 2855, 2209, 1666, 1604, 1462, 1377, 1269, 768 cm^{-1}; UV (EtOH) λ_{max} 264.5 (ε = 5084), 325 (ε = 5469) nm.

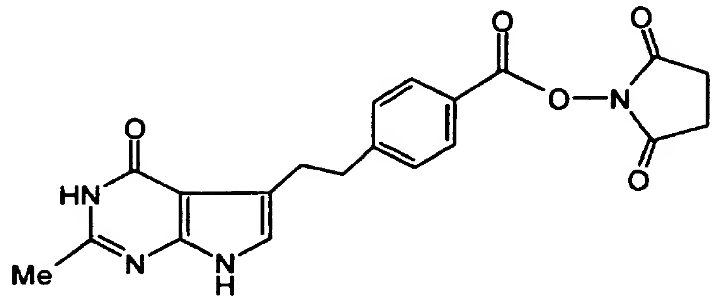
<u>Step 8</u>: Synthesis of 4-{[2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl]eth-2-yl}benzoic acid (a compound of formula (IV))



A mixture of the acetylene of Step 7 (3.1 g, 10.58 mmol) and 5% Pd/C (1.5 g) in dimethylformamide (150 mL) was stirred under 60 psi (414 kPa) H_2 at 50°C for 24 hours The mixture was filtered through Celite® 521 filter agent to remove the catalyst, and the filtrate concentrated to ~1/5 of its original volume. Methanol (25 mL) was added to precipitate a solid which was filtered, washed with methanol (25 mL) and dried to give the product as a gray solid (1.45 g, 46%).

^1H NMR (DMSO-d_6) δ 12.70 (broad singlet, COOH), 11.59 (broad singlet, NH), 11.28 (broad singlet, NH), 7.84 (d, J = 8.09 Hz, ArH_2), 7.32 (d, J = 8.09 Hz, ArH_2), 6.64 (d, J = 1.84 Hz, Pyr H), 3.06 - 2.92 (m, CH_2CH_2), 2.29 (s, CH_3) ppm; IR (KBr) υ 3275, 2928, 2855, 1658, 1610, 1273, 1176, 1071 cm^{-1}; UV (EtOH) λ_{max} 223 (ε = 18330), 266.5 (ε = 10650) nm; MS (FAB) 298 (M^+, 15).

<u>Step 9</u>: Synthesis of 4-{[2-methyl-4-oxo-3H-pyrrolo[2,3-d]pyrimidin-5-yl]eth-2-yl}benzoic acid (N-succinimide ester) "Active Ester" (compound of formula (I))

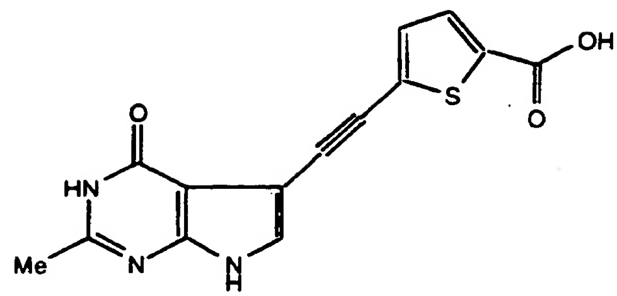


To a stirred solution of the carboxylic acid of Step 8 (1.3 g, 4.4 mmol) and N-Hydroxysuccinimide (756 mg, 6.6 mmol) in dimethylformamide (50 mL) at room temperature was added 1,3-dicyclohexylcarbodiimide (1.4 g, 6.7 mmol) under nitrogen. The reaction mixture was stirred for 24 hours and then filtered to remove dicyclohexylurea. The filtrate was concentrated in vacuo and the resulting residue sonicated in 20% methanol/ethyl acetate (50 mL) to produce a solid which was filtered, washed with ethyl acetate (75 mL) and dried to give the active ester as a gray solid (1.2 g, 69%).

^{1}H NMR (DMSO-d_6) δ 11.61 (broad singlet, NH), 11.27 (broad singlet, NH), 7.99 (d, J = 8.46 Hz, ArH_2), 7.46 (d, J = 8.46 Hz, ArH_2), 6.63 (d, J = 1.84 Hz, Pyr H), 3.10 (t, J = 6.80 Hz, CH_2), 2.98 (t, J = 6.80 Hz, CH_2), 2.89 (bs, CH_2CH_2), 2.29 (s, CH_3) ppm; IR (KBr) υ 3115, 3070, 3001, 2935, 2855, 1771, 1741, 1653, 1609, 1235, 1207, 1069, 917 cm^{-1}; UV (EtOH) λ_{max} 204 (ε = 28116), 225 (ε = 29641), 283 (ε = 7500) nm; MS (FD) 394 (M^+, 100).

Preparation 2

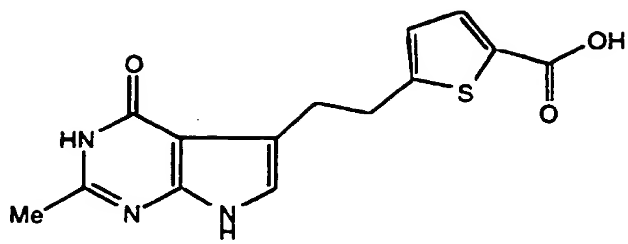
Step 1: Synthesis of 1-[2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl]-2-[2-carboxythien-5-yl]ethyne



A mixture of 2-methyl-3H-4-oxo-5-ethynepyrrolo-[2,3-d]pyrimidine made from steps 1-6 of Preparation 1 (2.25 g, 13.0 mmol), 2-bromothiophene-5-carboxylic acid (2.71 g, 13.0 mmol), and N,O-bis(trimethylsilyl)acetamide (11 mL, 44.6 mmol) in acetonitrile (65 mL) was heated at 40°C under nitrogen for 4 hours Triethylamine (3.4 mL, 24.4 mmol) was added and the mixture was deoxygenated with nitrogen for 20 minutes. A preformed catalyst mixture containing palladium chloride (119 mg, 0.67 mmol), and triphenylphosphine (347 mg, 1.32 mmol) in acetonitrile (10 mL) was added and the resulting mixture was heated at reflux for 3 hours The reaction mixture was then cooled to 0°C and water (1.8 mL) added dropwise causing a precipitate to form which was filtered, washed with acetonitrile, and dried to give the product as a gray solid (3.57 g, 92%).

^1H NMR (DMSO-d_6) δ 13.32 (broad singlet, COOH), 12.18 (broad singlet, NH), 11.92 (broad singlet, NH), 7.67 (d, J = 3.68 Hz, ThH), 7.51 (d, J = 2.57 Hz, Pyr H), 7.31 (d,-J = 3.68 Hz, ThH), 2.32 (s, CH_3) ppm; IR (KBr) υ 3125, 2207, 1673, 1420, 1369, 1293, 816, 749 cm^{-1}; UV (EtOH) λ_{max} 271 (ε =376), 321 (ε = 164), 326 (ε = 157) nm; MS (FD) 299 (M^+, 60).

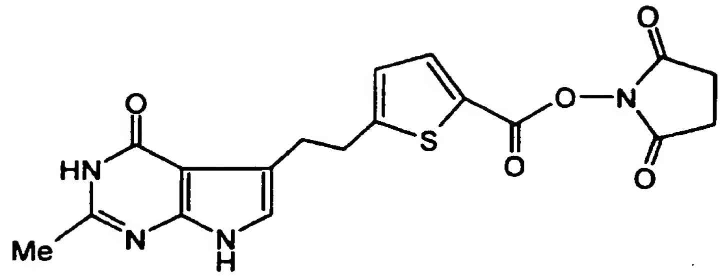
Step 2: Synthesis of (2-[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-yl)carboxylic acid



A mixture of the acetylene from Preparation 2, step 1 (3.4 g, 11.26 mmol) and 5% Pd /C (3.4 g) in dimethylformamide (75 mL) was stirred under 60 psi (414 kPa) H_2 at 50°C for 24 hours. The mixture was filtered through Celite® 521 filter agent to remove catalyst, and the filtrate concentrated to ~1/5 of its original volume. Methanol (25 mL) was added to precipitate a solid which was filtered, washed with methanol (25 mL) and dried to give the product as a gray solid (1.26 g, 37%).

^{1}H NMR (DMSO-d_6) δ 12.73 (broad singlet, COOH), 11.62 (broad singlet, NH), 11.33 (broad singlet, NH), 7.53 (d, J = 3.68 Hz, ThH), 6.89 (d, J = 3.68 Hz, ThH), 6.70 (d, J = 2.21 Hz, Pyr H), 3.23 (t, J = 7.35 Hz, CH_2), 2.98 (t, J= 7.54 Hz, CH_2), 2.29 (s, CH_3) ppm; IR (KBr) υ 3113, 2928, 2854, 1657, 1537, 1459, 1268, 1098, 814, 755 cm^{-1}; UV (EtOH) λ_{max} 218.5 (ε = 15236), 278.5 (ε = 15258), 361.5 (ε = 2525) nm; MS (FAB) 304 (M^+, 60).

__Step 3__: Synthesis of (2-[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-yl)carboxylic acid (N-succinimide ester) "Active Ester" (compound of formula I)



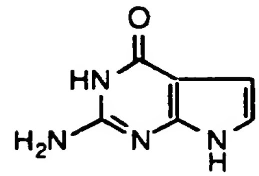
To a stirred solution of the carboxylic acid from Preparation 2, step 2 (1.2 g, 3.8 mmol) and N-hydroxysuccinimide (661 mg, 5.8 mmol) in N,N-dimethylformamide (40 mL) was added 1,3-dicyclohexylcarbodiimide (1.2 g, 5.8 mmol) at room temperature under nitrogen. The mixture was stirred at room temperature for 24 hours and then filtered to remove dicyclohexylurea. The filtrate was concentrated in vacuo and the resulting residue sonicated in 20% methanol/ethyl acetate (50 mL) to produce a solid which was filtered, washed with ethyl acetate (75 mL) and dried to give the active ester as a gray solid (950 mg, 59%).

^{1}H NMR (DMSO-d_6) δ 11.64 (broad singlet, NH), 11.34 (broad singlet, NH), 7.94 (d, J = 4.04 Hz, ThH), 7.08 (d, J = 4.04 Hz, ThH), 6.72 (d, J = 2.21 Hz, Pyr H), 3.38 - 3.30 (m,-CH_2), 3.06 - 3.00 (m, CH_2), 2.86 (broad singlet,CH_2CH_2), 2.29 (s, CH_3) ppm; IR (KBr) υ 3112, 3073, 2931, 2854, 1740, 1653, 1447, 1366, 1204, 1066, 814 cm^{-1}; UV (EtOH) λ_{max} 217.5 (ε = 15722), 262.0 (ε = 14769), 286.5 (ε = 18291) nm; MS (FD) 400 (M^+, 100).

Preparation 3

Preparation of {2-fluoro-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)-eth-2-yl]}benzoic acid (N-succinimide ester)

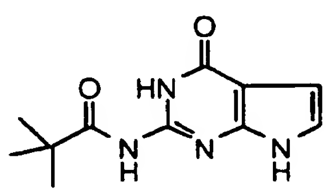
Step 1: Synth sis of 2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidine



To a suspension of 2,4-diamino-6-hydroxypyrimidine (40 g, 317 mmol) in H_2O (400 mL) was added $NaHCO_3$ (66.61 g, 793 mmol) and the mixture was heated to 50°C. Chloroacetaldehyde (50% in H_2O, 28.6 g, 46 mL, 365 mmol) was added dropwise over 40 min, and the reaction was stirred for 1 hour. The mixture was cooled to 5-10°C and the product filtered. The filtered product was washed with H_2O, reslurried with H_2O (130 mL), filtered and dried to give 36.24 g product (76%) as a brown solid.

^{1}H NMR (DMSO-d_6) δ 10.95 (s, NH), 10.21 (s, NH), 6.59 (s, PyrH), 6.16 (s, PyrH), 6.03 (s, NH_2) ppm; IR (KBr) υ_{max} 3448, 3361, 3224, 3119, 2924, 1658, 1622, 1427, 1376, 1356, 823 cm^{-1}; UV (MeOH) λ_{max} 214.75 (ε = 16432), 258.25 (ε = 9687) nm; MS (FD) m/z 150 (M^+, 100);

Step 2: Synthesis of 2-t-butylacetamidyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidine

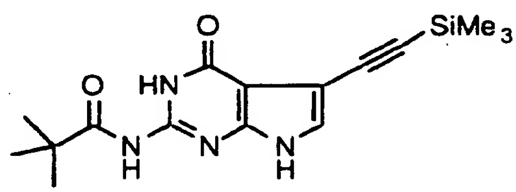


A mixture of 2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidine (33.5 g, 223 mmol), pivalic anhydride (166.2 g, 180 mL, 893 mmol), and 4-dimethylaminopyridine (1.36 g, 11.1 mmol) was heated to 120°C and stirred for 2 hours The

reaction was cooled to 40°C, and added to Et_2O (400 mL) with stirring. The precipitated product was filtered, washed with Et_2O, reslurried in Et_2O (300 mL), filtered and dried to give 36.72 g product (70%) as a tan solid.

^1H NMR (DMSO-d_6) δ 11.83 (s, NH), 11.58 (s, NH), 10.80 (s, NH), 6.94 (t, J = 2.7 Hz, PyrH), 6.40 (d, J = 2.04 Hz, PyrH), 1.26 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3300, 3219, 2968, 1655, 1569, 1430, 1242, 1170, 802 cm^{-1}; UV (MeOH) λ_{max} 217.75 (ε = 13121), 272.75 (ε = 11683) nm; MS (FD) m/z 234 (M^+, 100);

Step 3: Synthesis of 2-t-butylacetamidyl-3H-4-oxo-5-(trimethylsilylethyne)-pyrrolo[2,3-d]pyrimidine

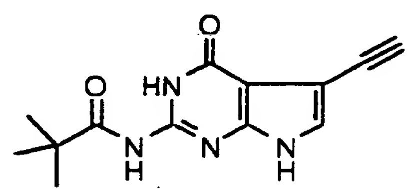


To a suspension of 2-t-butylacetamidyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidine (32.9 g, 140 mmol) in DMF (125 mL) was added N,O-bis(trimethylsilyl)acetamide (62.8 g, 76 mL, 309 mmol) and the reaction was stirred at 40°C for 1.5 hours The reaction was then cooled to 0°C and N-iodosuccinimide (37.9 g, 168 mmol) was added. The resulting mixture was stirred for 2 hr while gradually warming to RT. In a separate flask, a mixture of palladium(II) chloride (2.49 g, 14.0 mmol) and triphenylphosphine (7.37 g, 28.1 mmol) in DMF (25 mL) was stirred at RT for 30 minutes. Copper(I) iodide (2.67 g, 14.0 mmol), triethylamine (17.0 g, 23.5 mL, 168 mmol) and (trimethylsilyl)acetylene (25.0 g, 254 mmol) were added to the pyrrolopyrimidine reaction, followed by the triphenylphosphine-palladium chloride mixture. The resulting mixture was stirred at RT for 18 hr, then diluted with CH_3CN (1000 mL) and filtered to remove any insoluble material. Water (31 mL) was then added with stirring, and

the resulting solid was filtered, washed with CH_3CN and dried in vacuo to give 23.84 g product (51%) as a brown solid.

^1H NMR (DMSO-d_6) δ 11.92 (s, NH), 11.84 (s, NH), 10.88 (s, NH), 7.31 (d, J = 1.93 Hz, PyrH), 1.23 (s, $3CH_3$), 0.19 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3228, 2154, 1677, 1660, 1619, 1582, 1434, 1244, 861, 793 cm^{-1}; UV (MeOH) λ_{max} 248.5 (ε = 13287), 284.75 (ε = 13539) nm; MS (FD) m/z 330 (M^+, 100);

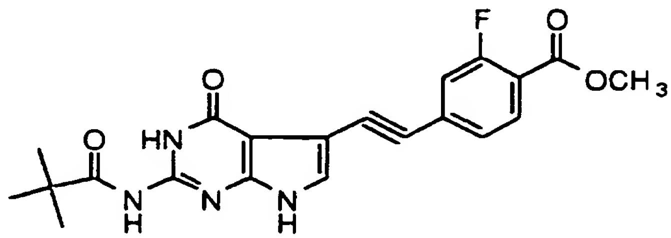
Step 4: Synthesis of 2-t-butylacetamidyl-3H-4-oxo-5-ethyne-pyrrolo[2,3-d]pyrimidine



To a solution of the 2-t-butylacetamidyl-3H-4-oxo-5-(trimethylsilylethyne)-pyrrolo[2,3-d]pyrimidine (19.55 g, 59.2 mmol) in DMF (150 mL) was added tetra-n-butylammonium fluoride (15.47g, 59.2 mmol) and the reaction was stirred at RT for 1.5 hours Acetic acid (4.4 mL) was added, followed by H_2O (200 mL). The resulting solid is filtered, washed with H_2O and dried in vacuo to give 12.94 g product (85%) as a brown solid.

^1H NMR (DMSO-d_6) δ 11.88 (s, NH), 11.85 (s, NH), 10.86 (s, NH), 7.31 (s, PyrH), 3.92 (s, CH), 1.22 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3233, 2113, 1683, 1649, 1617, 1580, 1432, 1240, 791 cm^{-1}; UV (MeOH) λ_{max} 234.75 (ε = 14417), 280.25 (ε = 14019) nm; MS (FD) m/z 258 (M^+, 100);

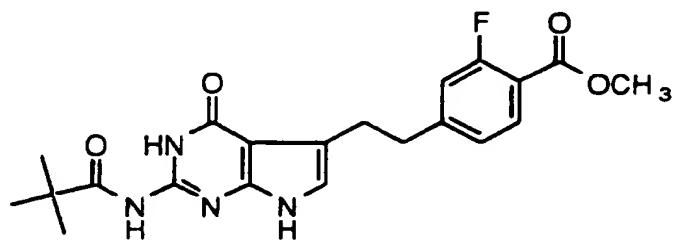
Step 5: Synthesis f 1-(2-t-butylacetamidyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)-2-(3-fluoro-4-carbonylmethoxyphenyl)ethyne



A mixture of 2-t-butylacetamidyl-3H-4-oxo-5-ethyne-pyrrolo[2,3-d]pyrimidine (10.0 g, 38.75 mmol), methyl 2-fluoro-4-iodobenzoate (11.9 g, 42.63 mmol), and bis-trimethylsilylacetamide (21 mL, 85.13 mmol) in acetonitrile (200 mL) was heated at 40°C under nitrogen for 2.5 hours. Tri-ethylamine (10 mL, 71.70 mmol) was added and the mixture was de-gassed for 20 minutes. Next a catalyst mixture containing palladium chloride (343 mg, 1.93 mmol), and tri-phenylphosphine (1.02 g, 3.87 mmol) in acetonitrile (35 mL) was added and the resulting mixture was refluxed for 2.5 hours After cooling to room temperature the reaction mixture was filtered and water (5.0 mL) was added dropwise causing a precipitate to form which was collected, rinsed with acetonitrile (125 mL) and dried to give the product as a tan solid (11.92 g, 75%)

^{1}H NMR (DMSO-d_6) δ 12.13 (s, NH), 11.93 (s, NH), 10.95 (s, NH), 7.94 (t, J = 8.01 Hz, ArH), 7.51 (s, ArH), 7.42 (s, ArH), 7.39 (s, ArH), 6.61 (s, PyrH), 3.87 (s, OCH3), 1.25 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3217, 1733, 1657, 1615, 1581, 1435, 1293, 1247, 1142, 1090, 791 cm^{-1}; MS (FD) *m/z* 410 (M^+, 100). Anal. Calcd. for $C_{21}H_{19}N_4O_4F$ requires: C, 64.54; H, 4.92; N, 10.26; F, 4.64%. Found: C, 60.76; H, 4.71; N, 13.43; F, 6.35%.

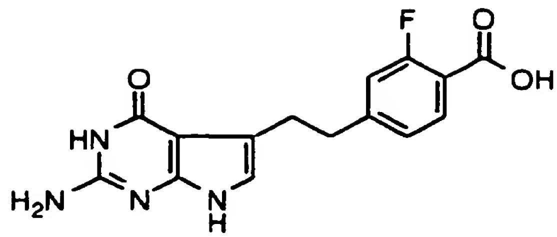
Step 6: Synthesis of (2-flu ro-4-[(2-t-butylac tamidyl-3H-4-xo-pyrrolo[2,3-d]pyrimidin-5-yl)-eth-2-yl]}benzoic acid methyl ester



A mixture of the acetylene from Preparation 3, Step 5 (11.9 g, 29.0 mmol) and 5% Pd/C (6.0 g) in DMF (140 mL) was stirred under 60 psi (414 kPa) H_2 at room temperature for 24 hours The mixture was passed through Celite® 521 to remove catalyst, the filtrate was concentrated to a small volume and methanol (50 mL) was added. The product was filtered, rinsed with methanol (75 mL) and dried to give a tan solid (7.1 g, 59%).

^1H NMR (DMSO-d_6) δ 11.77 (s, NH), 11.24 (s, NH), 10.77 (s, NH), 7.77 (t, J = 8.01 Hz, ArH), 7.2-7.1 (m, ArH_2), 6.63 (s, PyrH), 3.81 (s, OCH_3), 3.1-2.8 (m, CH_2CH_2), 1.23 (s, 3 CH_3) ppm; IR (KBr) υ_{max} 3290, 3228, 1739, 1721, 1653, 1615, 1588, 1533, 1438, 1304, 1240, 790 cm^{-1}; UV (EtOH) λ_{max} 229.5 (ε = 23424), 284.5 (ε = 14936) nm; MS (FAB) *m/z* 415 (M^+, 100). Anal. Calcd. for $C_{21}H_{23}N_4O_4F$ requires: C, 60.86; H, 5.59; N, 13.52; F, 4.58%. Found: C, 60.93; H, 5.66; N, 13.74; F, 4.52%.

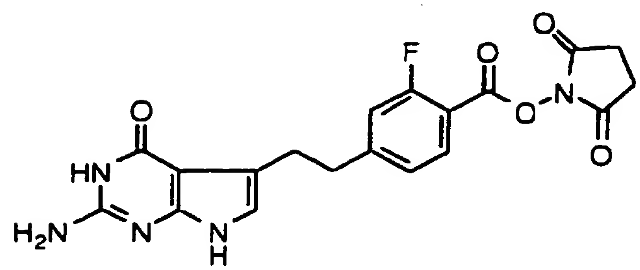
Step 7: Synthesis of (2-fluoro-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)-eth-2-yl]}benzoic acid:



The protected amino acid from Preparation 3, Step 6 (7.0 g, 16.9 mmol) was combined with p-toluenesulfonic acid (7.1 g, 37.2 mmol) in ethanol (235 mL) and refluxed overnight (18 h). After cooling to room temperature the solid was collected and rinsed with fresh ethanol. Without drying the solid was taken up in aqueous. NaOH (100 mL, 1N) and stirred at 45°C for 2 hours After cooling to room temperature the solution was adjusted to pH = 3 with aqueous. HCl (1N). The resulting solid was collected by suction filtration, rinsed with water then dried to give the product as a tan solid (4.96 g, 94%).

^{1}H NMR (DMSO-d_6) δ 13.02 (br s, COOH), 10.62 (s, NH), 10.15 (s, NH), 7.74 (t, J = 7.87 Hz, ArH), 7.10 (d, J = 9.84 Hz, ArH), 6.31 (s, PyrH), 6.00 (s, NH_2), 3.02-2.90 (m, CH_2), 2.88-2.80 (m, CH_2) ppm; IR (KBr) υ_{max} 3614, 3475, 3210, 2925, 1669, 1536, 1421, 1305, 1231, 1162, 1082 cm^{-1}; UV (EtOH) λ_{max} 202.5 (ε = 28206), 225 (ε = 24803), 263.5 (ε = 12113) nm; and MS (FAB) m/z 317 (M^+, 85).
Anal. Calcd. for $C_{15}H_{13}N_4O_3F$ requires: C, 56.96; H, 4.14; N, 17.71; F, 6.01%. Found: C, 53.06; H, 4.14; N, 16.65; F, 5.20%.

Step 8: Synthesis of {2-fluoro-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)-eth-2-yl]}benzoic acid (N-succinimide ester):



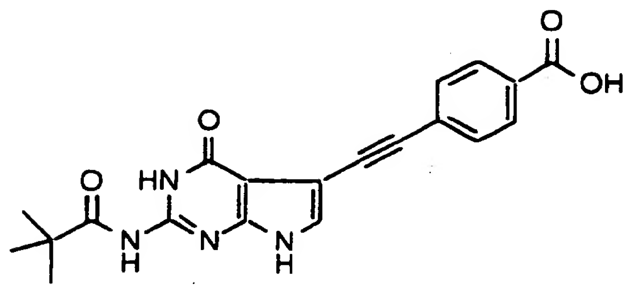
A mixture of the acid from Preparation 7, Step 3 (4.80 g, 15.2 mmol), N-hydroxysuccinimide (2.10 g, 18.3 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (3.50 g, 18.3 mmol) in DMF (80 mL) was stirred at room temperature under nitrogen for 24 hours The reaction mixture was concentrated and the residue was sonicated in aqueous. HCl (100 mL, 1N). The solid was filtered, rinsed with water (150 mL) and dried to give the ester as a yellow solid (5.83 g, 92%).

^{1}H NMR (DMSO-d_6) δ 10.64 (s, NH), 10.17 (s, NH), 7.93 (t, J = 7.68 Hz, ArH), 7.31 (d, J = 12.34 Hz, ArH), 7.25 (d, J = 7.79 Hz, ArH), 6.31 (s, PyrH), 6.07 (s, NH_2), 3.15-3.00 (m, CH_2), 2.99-2.79 (m, CH_2CH_2, $ArCH_2$) ppm; IR (KBr) υ_{max} 3367, 3216, 1773, 1733, 1633, 1540, 1427, 1206, 1068, 993 cm^{-1}; UV (EtOH) λ_{max} 222 (ε = 20758), 246 (ε = 21424) nm; and MS (FAB) *m/z* 414 ($M^{\cdot}$, 100). Anal. Calcd. for $C_{19}H_{16}N_5O_5F$ requires: C, 55.21; H, 3.90; N, 16.94%. Found: C, 52.14; H, 4.01; N, 15.94%.

Preparation 4

Preparation of 4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)-eth-2-yl]benzoic acid (N-succinimide ester)

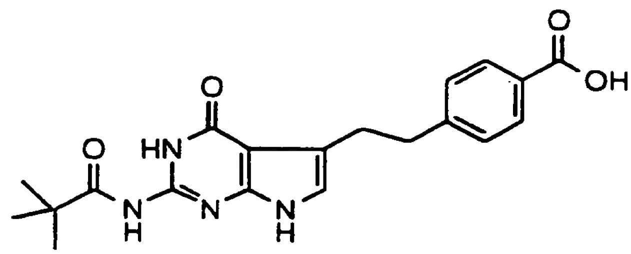
Step 1: Synthesis of 4-[(2-t-butylacetamidyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)-ethyn-2-yl]benzoic acid:



To a solution of the acetylene from Preparation 3, Step 4 (258 mg, 1.0 mmol) and 4-iodobenzoic acid (248 mg, 1.0 mmol) in CH_3CN (4 mL) was added N-O-bis(trimethylsilyl)acetamide (671 mg, 0.82 mL, 3.3 mmol) and the reaction was stirred at 40°C for 2 hours In a separate flask, a mixture of palladium(II) chloride (9 mg, 0.05 mmol) and triphenylphosphine (26 mg, 0.1 mmol) in DMF (1 mL) was stirred at RT for 90 minutes. Triethylamine (182 mg, 0.25 mL, 1.8 mmol) was added to acetylene mixture followed by the triphenylphosphine-palladium chloride mixture. The reaction was then refluxed for 2 hr, cooled and H_2O was added (1 mL containing 6-8 drops of 1N HCl). The resulting solid was filtered, washed with CH_3CN and dried in vacuo. The crude product was purified by flash chromatography on silica gel (0.25% AcOH/10% MeOH/CH_2Cl_2) to give 111 mg product (29%) as a tan solid.

^1H NMR (DMSO-d_6) δ 12.08 (s, NH), 11.92 (s, NH), 10.92 (s, NH), 7.93 (d, J = 8.13 Hz, ArH_2), 7.52 (d, J = 8.1 Hz, ArH_2), 7.46 (s, PyrH), 1.24 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3221, 2974, 2213, 1658, 1605, 1580, 1435, 1409, 1308, 1287, 1169, 788 cm^{-1}; UV (MeOH) λ_{max} 269 (ε = 19512), 322 (ε = 23843) nm; MS (FAB) m/z 379 (M^{+1}, 26).

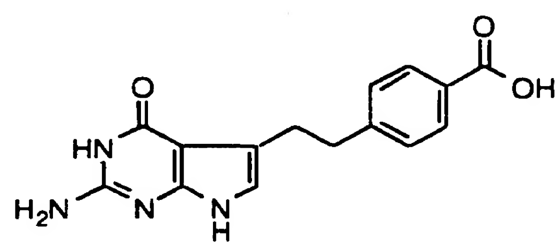
Step 2: Synthesis of 4-[(2-t-butylacetamidyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)-eth-2-yl]benzoic acid:



To a solution of acetylene from Preparation 4, Step 1 (497 mg, 1.31 mmol) in methanol (15 mL) was added 5% Pd/C (250 mg) and the mixture was stirred under 60 psi (414 kPa) H_2 at 50°C for 24 hours The reaction was filtered, concentrated in vacuo and triturated with methanol. The resulting solid was filtered and dried to give 232 mg product (46%) as off-white solid.

^{1}H NMR (DMSO-d_6) δ 11.76 (s, NH), 11.24 (s, NH), 10.77 (s, NH), 7.83 (d, J = 8.01 Hz, ArH_2), 7.31 (d, J = 8.08 Hz, ArH_2), 6.64 (s, PyrH), 3.01-2.87 (m, CH_2CH_2), 1.23 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3286, 3228, 2967, 1652, 1614, 1436, 1420, 1240, 1176, 789 cm^{-1}; UV (MeOH) λ_{max} 228.25 (ε = 20859), 295.25 (ε = 12430) nm; MS (FAB) m/z 383 (M^{+1}, 55).

<u>Step 3:</u> Synthesis of 4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)-eth-2-yl]benzoic acid:

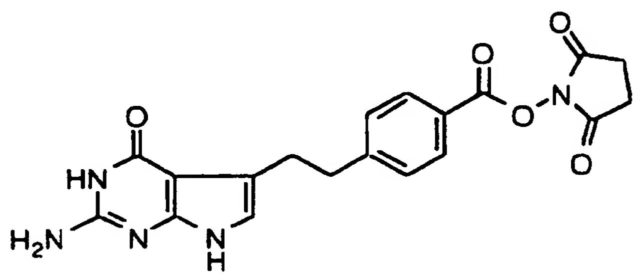


To a solution of protected amine from Preparation 4, Step 2 (5.76 g, 15.1 mmol) in EtOH (200 mL) was added p-toluenesulfonic acid monohydrate (6.30 g, 33.1 mmol) and the

mixture was stirred at reflux for 16 hours The reaction was cooled and the resulting precipitate was filtered, washed with EtOH and dried in vacuo to give 5.22 g product as tosic acid salt (74%). A sample was dissolved in aqueous LiOH and the solution was acidified to pH 3 with 1N HCl, the solid was filtered, washed with H_2O and dried in vacuo to give product as a tan solid.

^1H NMR (DMSO-d_6) δ 10.61 (s, NH), 10.14 (s, NH), 7.82 (d, J = 7.99 Hz, ArH_2), 7.30 (d, J = 7.99 Hz, ArH_2), 6.30 (s, PyrH), 5.99 (s, NH_2), 3.00 - 2.81 (m, CH_2CH_2) ppm; IR (KBr) υ_{max} 3475, 3209, 2923, 1665, 1389, 1289 cm^{-1}; UV (MeOH) λ_{max} 223.75 (ε = 24465) nm; MS (FAB) *m/z* 299 (M^{-1}, 8).

<u>Step 4</u>: Synthesis of 4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)-eth-2-yl]benzoic acid (N-succinimide ester):



To a solution of acid from Preparation 4, Step 4 (10.0 g, 33.5 mmol) and N-hydroxysuccinimide (4.24 g, 36.9 mmol) in DMF (150 mL) was added 1,3-dicyclohexylcarbodiimide (7.61 g, 36.9 mmol) and the reaction was stirred at RT overnight. After 20 hr, the mixture was filtered and the clear solution concentrated in vacuo. The crude product was triturated with 20% iPrOH/EtOAc and filtered, then triturated again and dried in vacuo to give 10.36 g product (76%) as off-white solid.

^1H NMR (DMSO-d_6) δ 10.61 (s, NH), 10.18 (s, NH), 7.97 (d, J = 8.06 Hz, ArH_2), 7.44 (d, J = 8.07 Hz, ArH_2), 6.29 (s, PyrH), 6.02 (s, NH_2), 3.10-3.03 (m, CH_2), 2.92-2.84 (m, CH_2), 2.88 (s, $2CH_2$) ppm; IR (KBr) υ_{max} 3367, 1773, 1735, 1661, 1633, 1378, 1211, 1072, 979 cm^{-1}; UV (MeOH) λ_{max} 222.5 (ε = 20997), 249.75 (ε = 25447) nm; MS (FD) m/z 395 (M^+, 100); Anal. Calcd. for $C_{19}H_{17}N_5O_5$ requires: C, 57.72; H, 4.33; N, 17.71%. Found: C, 57.54; H, 4.43; N, 17.42%.

Preparation 5

NOTE: In all of Preparation 5, "active ester" refers to succinimide ester made by the preparation described in any of Preparation 1, 2, 3 or 4; and the term amine refers to an amine of Formula II (namely: HNR^1R^2, where R^1 and R^2 are as described previously).

5A. Rapid Analogue Process (RAP) General Procedure A

A mixture of active ester (0.126 mmol), amine (0.38 mmol), and N,O-bis(trimethylsilyl)acetamide (0.2 mL, 0.81 mmol) in dry dimethylformamide (3 mL) is heated at 55°C under nitrogen for 18-48 hours. The reaction is quenched with 1N aqueous HCl (0.05 mL) then the solvent is removed in vacuo to give a residue which is azeotroped with xylenes (6 mL) and dried under high vacuum to remove any remaining traces of solvent. The residue is sonicated with 1N aqueous HCl (15 mL) for ~0.5 hours and the resulting solid is filtered, washed with water (5 mL), diethyl ether (5 mL) and dried to give the desired product as a solid.

5B. Rapid Analogue Process (RAP) General Procedure B

A mixture of active ester (0.126 mmol), amine (0.38 mmol), and N,O-bis(trimethylsilyl)acetamide (0.2 mL, 0.81 mmol) in dry dimethylformamide (3 mL) is heated at 55°C

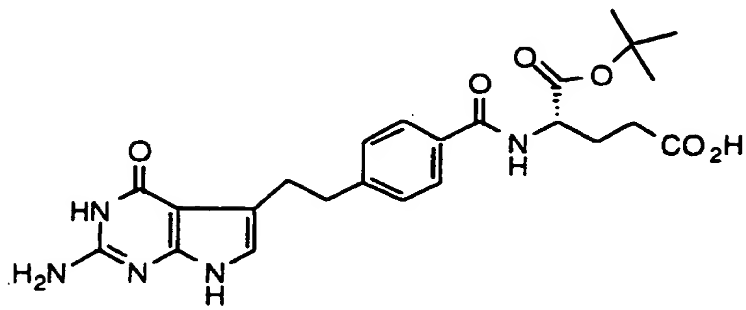
under nitrogen for 18 hours. Ethylenediamine (~20 equivalents) is added and the solution stirred at 55°C for a further 0.5 hours The reaction is then quenched with 1N aqueous HCl (0.05 mL) then the solvent is removed in vacuo to give a residue which is azeotroped with xylenes (6 mL) and dried under high vacuum to remove any remaining traces of solvent. The residue is sonicated with 1N aqueous HCl (15 mL) for ~0.5 hours and the resulting solid is filtered, washed with water (5 mL), diethyl ether (5 mL) and dried to give the desired product as a solid.

5C. Rapid Analogue Process (RAP) General Procedure C

To a solution of active ester (0.126 mmol) in dimethylformamide (3 mL) is added a solution of amino acid (0.634 mmol) in 1N aqueous NaOH (0.634 mmol) and the solution heated at 55°C under nitrogen for 18 hours The reaction is then quenched with 1N aqueous HCl (2 mL). Then the solvent is removed in vacuo to give a residue which is azeotroped with xylenes (6 mL) and dried under high vacuum to remove any remaining traces of solvent. The residue is sonicated with 1N aqueous HCl (15 mL) for ~0.5 hours and the resulting solid is filtered, washed with water (5 mL), diethyl ether (5 mL) and dried to give the desired product as a solid.

Preparation 6

Preparation of starting material for L-glutamic acid that is used in Preparation 7: Sulfonamide Coupling General Procedure D



Active ester made using Preparation 4 (7.59 g, 19.2 mmol) and L-glutamic acid-α-t-butyl ester (5.85 g, 28.8 mmol) were reacted according to General Procedure 5A for 16 hours to give the α-t-butyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimid-5-yl)-eth-2-yl]benzoyl-L-glutamic acid product as a green solid (9.1 g, 98%).

^{1}H NMR (DMSO-d_6) δ 10.59 (br s, NH), 10.38 (br s, NH), 7.78 (d, J = 8.15 Hz, ArH_2), 7.26 (d, J = 8.03 Hz, ArH_2), 6.29 (s, PyrH), 6.12 (br s, NH_2), 4.27-4.21 (m, CH), 2.99-2.80 (m, CH_2CH_2), 2.24 (t, J = 6.34 Hz, CH_2), 2.05-1.89 (m, CH_2), 1.39 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3345, 1639, 1539, 1369, 1155 cm^{-1}; UV (EtOH) λ_{max} 224 (ε = 22632) nm; MS (FAB) *m/z* 483 (M^+, 15).

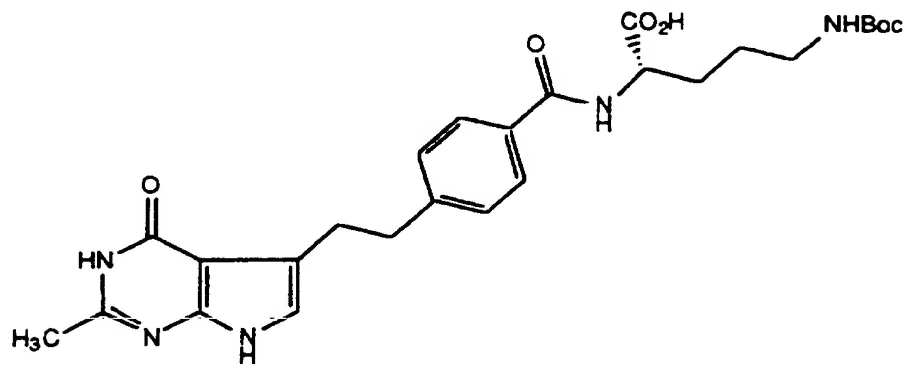
Preparation 7

Sulfonamide Coupling General Procedure D

A mixture of L-glutamic acid (1 equ) made using Preparation 6, sulfonamide (3 equ) and N,N-dimethylaminopyridine (1 equ) in dimethylformamide is treated with dicyclohexylcarbodiimide (1.5 equ) and stirred at RT overnight. The reaction is filtered, and the solvent was removed in vacuo. The resulting crude product is purified by flash chromatography (MeOH/CH_2Cl_2 mixtures with 0.5% AcOH) on silica gel to give the desired product as a solid.

Example 1

Synthesis of N-α-4-[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)-eth-2-yl]-benzoyl-N-Δ-BOC-L-ornithine

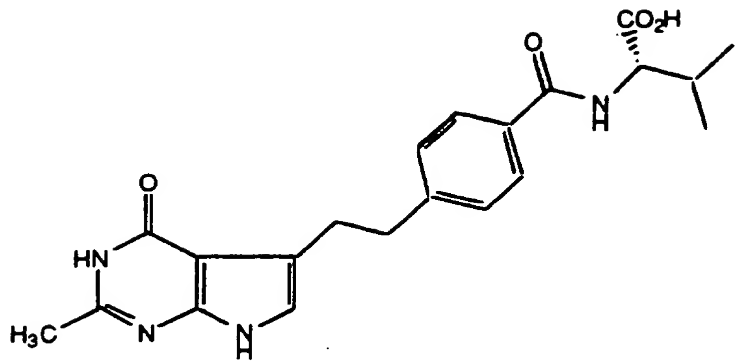


Active ester from Preparation 1, Step 9 (50 mg, 0.13 mmol) and L-Boc-ornithine (88 mg, 0.38 mmol) were reacted according to General Procedure 5A to give the product as a gray solid (40 mg, 61%).

^1H NMR (DMSO-d_6) δ 12.52 (broad singlet, COOH), 11.59 (broad singlet, NH), 11.27 (broad singlet, NH), 8.48 (d, J = 7.35 Hz, NH), 7.79 (d, J = 8.09 Hz, ArH_2), 7.29 (d, J = 8.46 Hz, ArH_2), 6.79 (t, J = 5.15 Hz, NH), 6.62 (s, Pyr H), 4.38 - 4.29 (m, CH), 3.03-2.89 (m, CH_2CH_2, CH_2N), 2.29 (s, CH_3), 1.88-1.63 (m, CH_2), 1.56 - 1.41 (m, CH_2), 1.37 (s, 9 H Boc) ppm; IR (KBr) υ 3318, 2932, 2859, 1685, 1529, 1505, 1448, 1366, 1290, 1251, 1168 cm^{-1}; MS (FAB) 512 (M^+, 25).

Example 2

Synthesis of N-4-[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)-eth-2-yl]-benzoyl-L-valine:

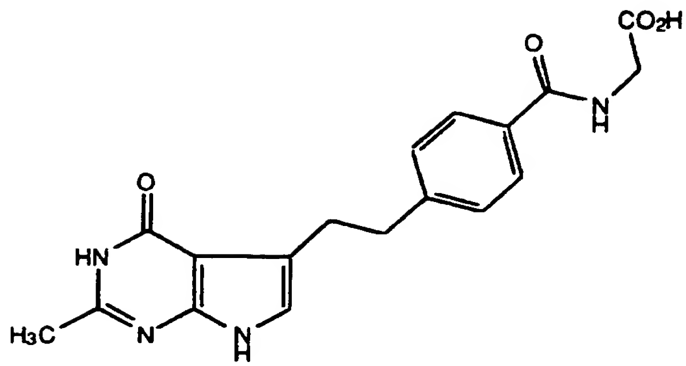


Active ester from Preparation 1, Step 9 (50 mg, 0.13 mmol) and L-valine (74 mg, 0.63 mmol) were reacted according to General Procedure 5A to give the product as a gray solid (28 mg, 55%).

^{1}H NMR (DMSO-d_6) δ 12.55 (broad singlet, COOH), 11.58 (broad singlet, NH), 11.26 (broad singlet, NH), 8.30 (d, J = 8.09 Hz, NH), 7.79 (d, J = 8.09 Hz, ArH_2), 7.29 (d, J = 8.09 Hz, ArH_2), 6.63 (d, J = 1.84 Hz, Pyr H), 4.27 (t, J = 7.36 Hz, CH), 3.03 - 2.93 (m, CH_2CH_2), 2.28 (s, CH_3), 2.23 - 2.15 (m, CH), 0.96 (t, J = 6.07 Hz, 2 CH_3) ppm; IR (KBr) υ 3140, 2965, 2932, 2857, 1653, 1610, 1528, 1500, 1447, 1296, 812 cm^{-1}; MS (FAB) 397 (M^+, 70).

Example 3

Synthesis of N-4-[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl-eth-2-yl]-benzoylglycine

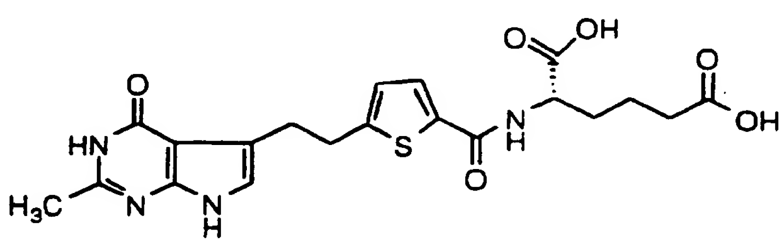


Active ester from Preparation 1, Step 9 (50 mg, 0.13 mmol) and glycine (48 mg, 0.64 mmol) were reacted according to General Procedure 5A to give the product as a tan solid (34 mg, 75%).

^{1}H NMR (DMSO-d_6) δ 11.64 (s, NH), 11.30 (s, NH), 8.76 (t, J = 5.88 Hz, NH), 7.78 (d, J = 8.09 Hz, Ar 2 H), 7.30 (d, J = 8.09 Hz, Ar 2 H), 6.63 (d, J = 2.21 Hz, Pyr H), 3.91 (d, J = 5.88 Hz, NCH_2), 3.04 - 2.92 (m, CH_2CH_2), 2.29 (s, CH_3) ppm; IR (KBr) υ 3291, 3152, 2926, 2365, 1668, 1642, 1542, 1505, 1410, 1232, 1110, 913 cm^{-1}; MS (FAB) 355 (M^+, 60).

Example 4

Synthesis of N-{2-[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]-pyrimidin-5-yl)eth-2-yl]thiophen-5-yl}carbonyl-α-amino adipic acid

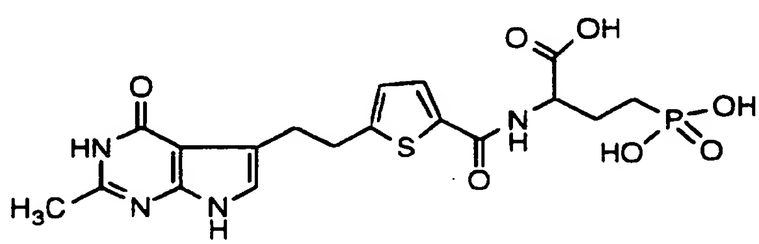


Active ester from Preparation 2, Step 3 (50 mg, 0.13 mmol) and α-aminoadipic acid (40 mg, 0.25 mmol) were reacted according to General Procedure 5A to give product as a yellow solid (13 mg, 23%).

^{1}H NMR (DMSO-d_6) δ 11.61 (broad singlet, NH), 11.31 (broad singlet, NH), 8.46 (d, J = 7.81 Hz, NH), 7.66 (d, J = 3.65 Hz, Th H), 6.82 (d, J = 3.57 Hz, Th H), 6.67 (s, Pyr H), 4.29-4.26 (m, CH), 3.22-2.86 (m, CH_2CH_2), 2.27 (s, CH_3), 1.82-1.63 (m, CH_2),1.63-1.45 (m, CH_2), 1.25-0.93 (m, CH_2) ppm; IR (KBr) υ 3114, 2932, 2856, 1654, 1452, 1294, 1234, 1072 cm^{-1}; MS (FAB) 447 (M^+, 25).

Example 5

Synthesis of N-{2-[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-yl}-carbonyl-2-amino-4-phosphonobutyric acid:



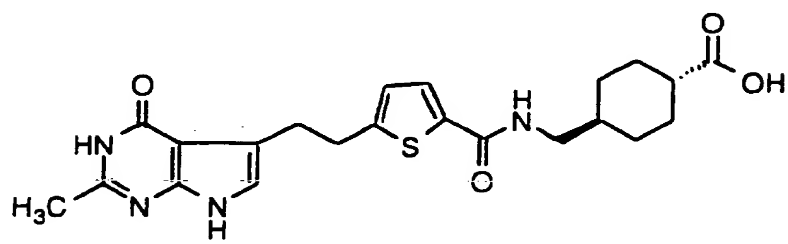
Active ester from Preparation 2, Step 3 (50 mg, 0.13 mmol) and DL-2-amino-4-phosphonobutyric acid (68 mg, 0.38 mmol) were reacted according to General Procedure 5A to give product as a gray solid (22 mg, 38%).

^{1}H NMR (DMSO-d_6) δ 11.61 (broad singlet, NH), 11.31 (broad singlet, NH), 8.72 (d, J = 7.47 Hz, NH), 7.68 (d, J = 3.57 Hz, Th H), 6.83 (d, J = 3.51 Hz, Th H), 6.68 (s, Pyr H), 4.34-4.29 (m, CH), 3.21-3.13 (m, CH_2), 2.99-2.91 (m, CH_2), 2.27 (s, CH_3), 2.03-1.87 (m, CH_2), 1.66-1.53 (m, CH_2) ppm; IR (KBr) υ 3148, 2931, 1699, 1661, 1549, 1520,

1451, 1234, 1043 cm^{-1}; UV (EtOH) λ_{max} 219.5 (ε = 16423), 280.5 (ε = 19355) nm; MS (FAB) 469 (M^+, 20).

Example 6

Synthesis of N-{2-[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]-pyrimidin-5-yl)eth-2-yl]-thiophen-5-yl}-carbonyl-trans-4-(aminomethyl)cyclohexanecarboxylic acid

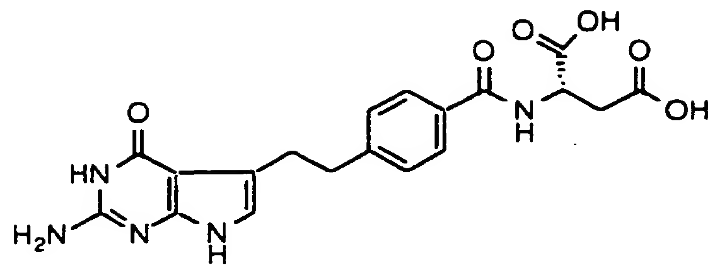


Active ester from Preparation 2, Step 3 (50 mg, 0.13 mmol) and trans-4-(aminomethyl)cyclohexane carboxylic acid (40 mg, 0.25 mmol) were reacted according to General Procedure 5A to give the product as a gray solid (13 mg, 23%).

^{1}H NMR (DMSO-d_6) δ 11.63 (broad singlet, NH), 11.34 (broad singlet, NH), 8.30 (t, J = 5.88 Hz, NH), 7.55 (d, J = 3.68 Hz, ThH), 6.82 (d, J = 3.68 Hz, ThH), 6.68 (s, Pyr H), 3.22-3.13 (m, CH_2), 3.08-2.93 (m, CH_2CH_2), 2.29 (s, CH_3), 2.19-2.07 (m, CH), 1.94-1.85 (m, CH_2), 1.79-1.70 (m, CH_2), 1.51-1.40 (m, CH), 1.33-1.17 (m, CH_2), 1.01-0.85 (m, CH_2) ppm; IR (KBr) υ 3114, 2929, 2855, 1692, 1644, 1546, 1521, 1439, 1275, 1234, 1094 cm^{-1}; UV (EtOH) λ_{max} 220.5 (ε = 13379), 279.5 (ε = 15680) nm; MS (FAB) 443 (M^+, 85).

Example 7

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-L-aspartic acid

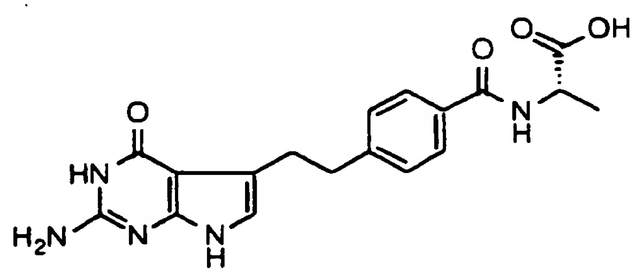


Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and L-aspartic acid (50 mg, 0.38 mmol), were reacted according to General Procedure 5A to give the product as a pink solid (43 mg, 83%).

^1H NMR (DMSO-d_6) δ 10.87 (broad singlet, NH), 10.67 (broad singlet, NH), 8.65 (d, J = 7.72, NH), 7.75 (d, J = 8.46, Ar H_2), 7.28 (d, J = 8.09, ArH_2), 6.38 (s, PyrH), 4.79-4.70 (m, CH), 3.01-2.93 (m, CH_2), 2.90-2.80 (m, CH_2), 2.75-2.65 (m, $\underline{CH_2}CO_2H$) ppm; IR (KBr) υ_{max} 3155, 2925, 1690, 1611, 1535, 1384, 1337, 1226, 1082 cm^{-1}; UV (EtOH) λ_{max} 203.5 (ε = 33841), 224.5 (ε = 23301), 242.5 (ε = 17789) nm; MS (FAB) *m/z* 414 (M^{+1}, 13).

Example 8

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-L-alanine



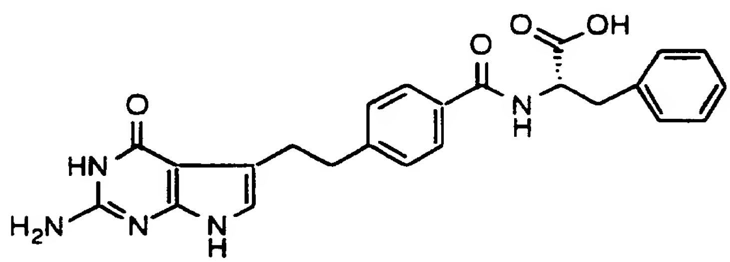
A mixture of the active ester Preparation 4, Step 4 (50 mg, 0.13 mmol) and L-alanine (34 mg, 0.38 mmol) were

reacted according to General Procedure 5A to give the product as a light pink solid (43 mg, 91%).

^{1}H NMR (DMSO-d_6) δ 11.18 (broad singlet, NH, NH), 8.56 (d, J = 7.35, NH), 7.79 (d, J = 8.09, ArH_2), 7.28 (d, J = 8.46, ArH_2), 6.44 (s, PyrH), 4.46-4.36 (m, CH), 3.00-2.84 (m, CH_2CH_2), 1.39 (d, J = 7.35, CH_3) ppm; IR (KBr) υ_{max} 3151, 2618, 1671, 1534, 1502, 1423, 1305, 1132 cm^{-1}; UV (EtOH) λ_{max} 202.5 (ε = 34951), 224.5 (ε = 23174) nm; MS (FAB) *m/z* 370 (M^{+1}, 100); Anal. Calcd. for $C_{18}H_{19}N_5O_4$ requires: C, 58.53; H, 5.18; N, 18.96%. Found: C, 50.26; H, 4.99; N, 16.57%.

Example 9

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-L-phenylalanine:



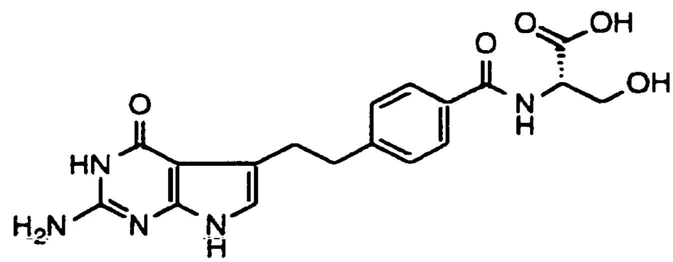
A mixture of the active ester Preparation 4, Step 4 (50 mg, 0.13 mmol) and L-phenylalanine (63 mg, 0.38 mmol) were reacted according to General Procedure 5A to give the product as an off-white solid (46 mg, 82%).

^{1}H NMR (DMSO-d_6) δ 10.67 (s, NH), 10.28 (broad singlet, NH), 8.59 (d, J = 7.72, NH), 7.70 (d, J = 8.09, ArH_2), 7.34-7.15 (m, ArH_2, ArH_5), 6.32 (s, PyrH), 4.64-4.56 (m, CH), 3.22-2.73 (m, CH_2CH_2, $\underline{CH_2}$Ph) ppm; IR (KBr) υ_{max} 3321, 2929, 1638, 1531, 1498, 1437, 1229, 1077 cm^{-1}; UV (EtOH) λ_{max} 202.5 (ε = 47012), 223 (ε = 26496) nm; MS (FAB) *m/z* 446 (M^{+1}, 45); Anal. Calcd. for $C_{24}H_{23}N_5O_4$ requires: C,

64.71; H, 5.20; N, 15.72%. Found: C, 60.72; H, 5.28; N, 14.82%.

Example 10

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-L-serine:

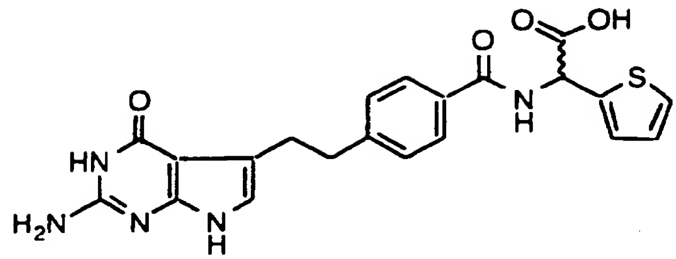


A mixture of the active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and L-serine (40 mg, 0.38 mmol) were reacted according to General Procedure 5A to give the product as a pink solid (40 mg, 82%).

^{1}H NMR (DMSO-d_6) δ 10.98 (broad singlet, NH), 10.85 (broad singlet, NH), 8.31 (d, J = 8.09, NH), 7.80 (d, J = 8.09, ArH_2), 7.29 (d, J = 8.09, ArH_2), 6.40 (s, PyrH), 4.49-4.43 (m, CH), 3.79 (d, J = 5.15, CH_2CO_2H), 3.00-2.84 (m, CH_2CH_2) ppm; IR (KBr) υ_{max} 3150, 2621, 1671, 1503, 1427, 1305, 1224, 1131, 1078 cm^{-1}; UV (EtOH) λ_{max} 202.5 (ε = 31105), 224.5 (ε = 21031) nm; MS (FAB) m/z 386 (M^{+1}, 26); Anal. Calcd. for $C_{18}H_{19}N_5O_5$ requires: C, 56.10; H, 4.97; N, 18.17%. Found: C, 50.04; H, 4.70; N, 16.34%.

Example 11

Synthesis of α-amino-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoylthiopheneacetic acid:

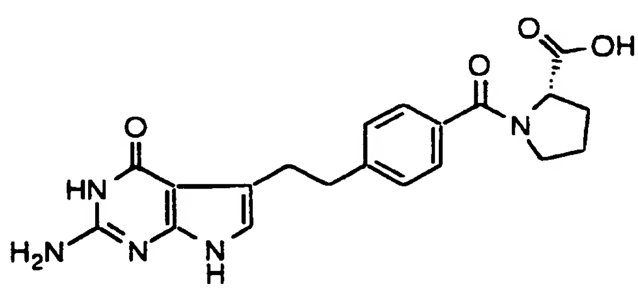


Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and DL-α-amino-2-thiopheneacetic acid (60 mg, 0.38 mmol) were reacted according to General Procedure 5C to give the product as a light brown solid (49 mg, 89%).

^{1}H NMR (DMSO-d_6) δ 10.73 (broad singlet, NH), 10.38 (broad singlet, NH), 9.13 (d, J = 7.72, NH), 7.84 (d, J = 8.09 ArH_2), 7.50 (d, J = 5.15, ThiH), 7.29 (d, J = 8.09, ArH_2), 7.18 (d, J = 3.31, ThiH), 7.03 (dd, J = 5.15, 3.68, ThiH), 6.35 (s, PyrH), 5.83 (d, J = 7.35, CH), 3.02-2.81 (m, CH_2CH_2) ppm; IR (KBr) υ_{max} 3328, 1687, 1527, 1496, 1380, 1230, 1078 cm^{-1}; UV (EtOH) λ_{max} 226.5 (ε = 26890) nm; MS (FAB) *m/z* 438 (M^{+1}, 4).

Example 12

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-L-proline:



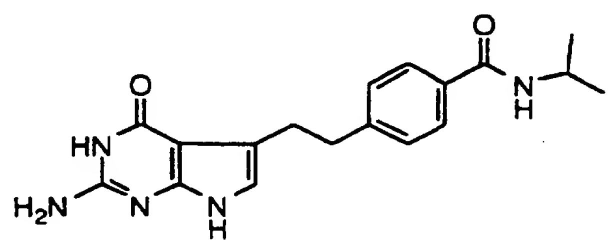
A mixture of the active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and L-proline (44 mg, 0.38 mmol)

were reacted according to General Procedure 5A to give the product as an off-white solid (25 mg, 50%).

^{1}H NMR (DMSO-d_6) δ 10.98 (broad singlet s, NH), 10.83 (broad singlet, NH), 7.44 (d, J = 8.09, ArH_2), 7.28 (d, J = 7.35, ArH_2), 6.42 (s, PyrH), 4.42-4.35 (m, CH), 3.61-3.43 (m, CH_2), 2.99-2.82 (m, CH_2CH_2), 2.55-2.45 (m, C<u>H</u>H), 2.30-2.20 (m, CH<u>H</u>), 1.93-1.79 (m, CH_2) ppm; IR (KBr) υ_{max} 3235, 2766, 1674, 1602, 1438, 1226, 1079 cm^{-1}; UV (EtOH) λ_{max} 202.5 (ε = 30942), 223.0 (ε = 24450), 251.5 (ε = 12966) nm; MS (FAB) *m/z* 396 (M^{+1}, 28).

Example 13

Synthesis of N-isopropyl-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzamide:



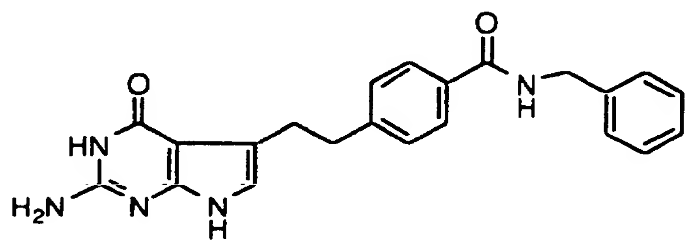
A mixture of the active ester from Preparation 4, Step 4 (75 mg, 0.19 mmol) and isopropyl amine (50 µL, 0.57 mmol) in CH_2Cl_2/MeOH was stirred at room temperature under nitrogen for 2.5 hours. The reaction was concentrated in vacuo, and the crude product was sonicated in aqueous HCl and filtered. The solid was sonicated in H_2O, the solid was filtered and dried to give the product as an off-white solid (42 mg, 66%).

^{1}H NMR (DMSO-d_6) δ 10.60 (s, NH), 10.16 (s, NH), 8.09 (d, J = 8.09, NH), 7.73 (d, J = 8.09, ArH_2), 7.25 (d, J = 8.46, ArH_2), 6.30 (s, PyrH), 6.01 (s, NH_2), 4.14-4.03 (m, CH), 2.99-2.93 (m, CH_2), 2.88-2.81 (m, CH_2), 1.15 (d, J =

6.62, $2CH_3$) ppm; IR (KBr) υ_{max} 3373, 3231, 2973, 2931, 1633, 1531, 1437, 1366, 1352 cm^{-1}; UV (EtOH) λ_{max} 203 (ε = 35708), 224.5 (ε-= 24191) nm; MS (FAB) m/z 340 (M^{+1}, 52).

Example 14

Synthesis of N-benzyl-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzamide

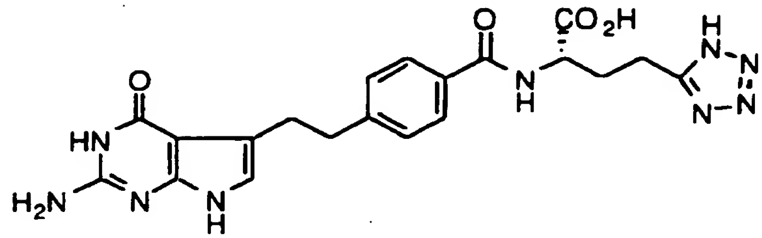


A mixture of the active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and benzyl amine (41 mg, 40 µL, 0.38 mmol) was reacted according to General Procedure 5A to give the product as a gray solid (43 mg, 88%).

^1H NMR (DMSO-d_6) δ 10.88 (broad singlet, NH), 10.67 (broad singlet, NH), 8.96 (t, J = 5.88, NH), 7.80 (d, J = 8.09, ArH_2), 7.36-7.22, m, ArH_2, ArH_5), 6.39 (s, PyrH), 4.47 (d, J = 4.04, $\underline{CH_2}Ph$), 3.01-2.82 (m, CH_2CH_2) ppm; IR (KBr) υ_{max} 3126, 2922, 1672, 1638, 1539, 1427, 1308, 1079 cm^{-1}; UV (EtOH) λ_{max} 203.5 (ε = 38228), 224 (ε = 23645) nm; MS (FAB) m/z 388 (M^{+1}, 28).

Example 15

Synthesis of γ-tetrazole-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-L-glutamic acid:

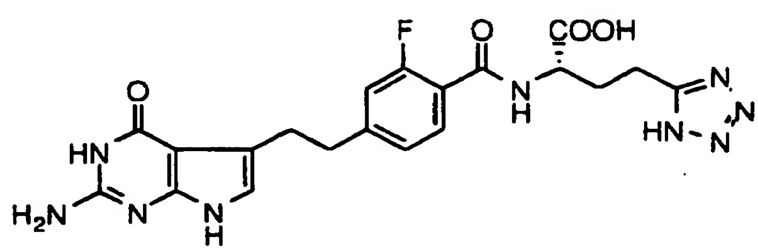


Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and L-glutamic acid γ-tetrazole hydrate (72 mg, 0.38 mmol) were reacted according to General Procedure 5C for 18 hours to give the product as an off white solid (52 mg, 91%).

^{1}H NMR (DMSO-d_6) δ 10.90 (s, NH), 10.69 (br s, NH), 8.65 (d, J = 7.72 Hz, NH), 7.81 (d, J = 8.09 Hz, ArH_2), 7.30 (d, J = 8.46 Hz, ArH_2), 6.39 (s, PyrH), 4.48-4.39 (m, CH), 3.04-2.83 (m, $3CH_2$), 2.38-2.14 (m, CH_2) ppm; IR (KBr) υ_{max} 3142, 1687, 1634, 1547, 1509, 1341, 1216, 1079 cm^{-1}; UV (EtOH) λ_{max} 224.5 (ε = 23605) nm; MS (FAB) *m/z* 452 (M^{+1}, 22).

Example 16

Synthesis of γ-tetrazole-N-{2-fluoro-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-L-glutamic acid:



The active ester from Preparation 3, Step 4 (50 mg, 0.13 mmol), and L-glutamic acid-γ-tetrazole (69 mg, 0.36

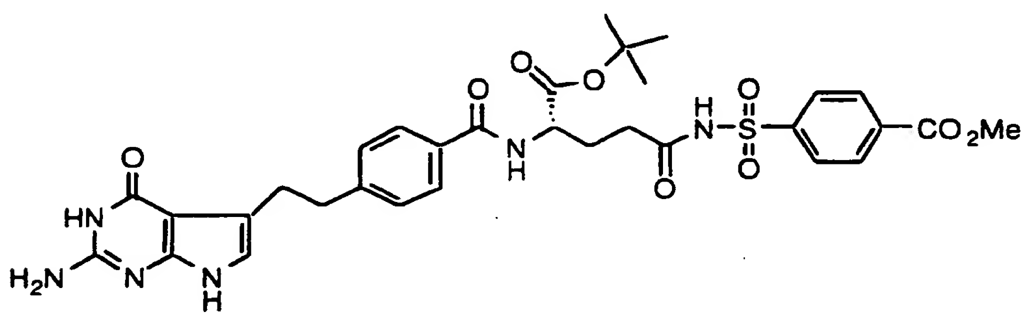
mmol) were react d according to General Procedure 5A for 16 hours to give the product as a brown solid (43 mg, 76%).

^{1}H NMR (DMSO-d_6) δ 11.18 (s, 2 NH), 8.55 (dd, J = 7.17, 5.51 Hz, NH), 7.54 (t, J = 7.60 Hz, ArH), 7.51-6.98 (br s, NH_2), 7.18-7.05 (m, ArH_2), 6.46 (s, PyrH), 4.49-4.38 (m, CH), 3.02-2.78 (m, CH_2CH_2), 2.43-2.12 (m, CH_2CH_2) ppm; IR (KBr) υ_{max} 3154, 1673, 1643, 1625, 1538, 1421, 1221, 1081, 764 cm^{-1}; MS (FAB) m/z 470 (M^{+1}, 60).

Example 17

Synthesis of γ-4-carboxyphenylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid

Step 1: Synthesis of γ-t-butyl-γ-4-carboxymethylphenylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoylglutamate:

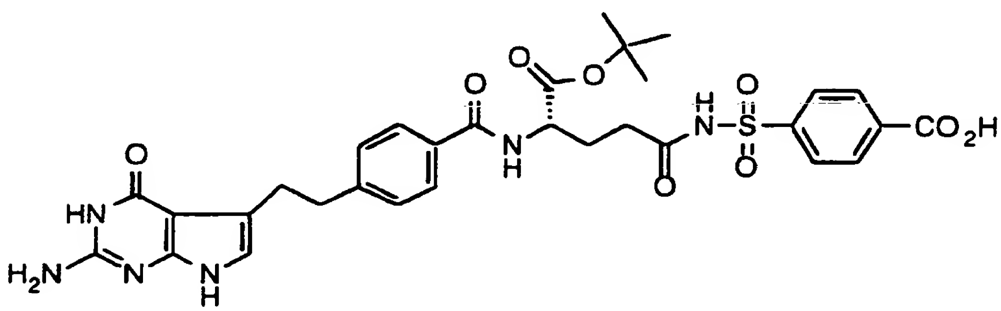


Carboxylic acid from Preparation 6 (500 mg, 1.03 mmol) and methyl 4-(aminosulfonyl)benzoate (668 mg, 3.10 mmol) were reacted according to the Sulfonamide Coupling Procedure of Preparation 7 for 16 hours to give the product as a white solid (326 mg, 46%).

^{1}H NMR (DMSO-d_6) δ 10.60 (s, NH), 10.13 (s, NH), 8.65-8.58 (m, NH), 8.04 (d, J = 8.36 Hz, ArH_2), 7.94 (d, J = 8.14 Hz,

ArH_2), 7.72 (d, J =8.08 Hz, ArH_2), 7.24 (d, J = 8.18 Hz, ArH_2), 6.30 (s, PyrH), 5.99 (br s, NH_2), 4.18-4.08 (m, CH), 3.86 (s, CH_3), 2.99-2.78 (m, CH_2CH_2), 2.30-2.21 (m, CH_2), 1.93-1.78 (m, CH_2), 1.36 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3362, 1730, 1661, 1634, 1538, 1437, 1369, 1282, 1154, 1086 cm^{-1}; UV (MeOH) λ_{max} 225 (ε = 33811) nm; MS (FAB) *m/z* 681 (M^{+1}, 23)

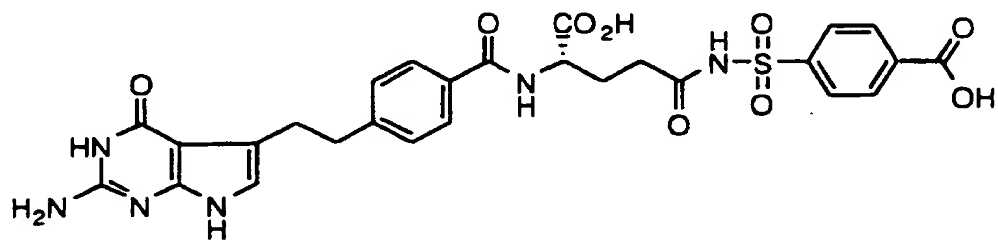
__Step 2:__ **Synthesis of γ-t-butyl-γ-4-carboxyphenylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid:**



A solution of methyl ester from Example 17, Step 1 (304 mg, 0.45 mmol) and 1N aqueous LiOH (1.11 mL, 1.11 mmol) in dioxane/H_2O (15 mL) was stirred at 100°C for 5 hours The reaction was cooled, concentrated to small volume, acidified to pH 2 and the resulting solid was filtered. The crude product was purified by flash chromatography (0.5% AcOH/15% MeOH/CH_2Cl_2) to give the product as a white solid (173 mg, 58%).

^1H NMR (DMSO-d_6) δ 10.61 (s, NH), 10.18 (s, NH), 8.86 (d, J = 6.17 Hz, NH), 7.94 (d, J = 8.18 Hz, ArH_2), 7.81 (d, J = 8.22 Hz, ArH_2), 7.73 (d, J = 8.02 Hz, ArH_2), 7.24 (d, J = 8.05 Hz, ArH_2), 6.31 (s, PyrH), 6.01 (br s, NH_2), 4.18-4.09 (m, CH), 2.99-2.84 (m, CH_2CH_2), 2.15 (t, J = 6.96 Hz, CH_2), 1.95-1.81 (m, CH_2), 1.38 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3359, 2931, 1636, 1543, 1404, 1369, 1253, 1153, 1085 cm^{-1}; UV (MeOH) λ_{max} 226.25 (ε = 30379) nm; MS (FAB) *m/z* 667 (M^{+1}, 2).

Step 3: Synthesis of γ-4-carboxyphenylsulf namyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid:



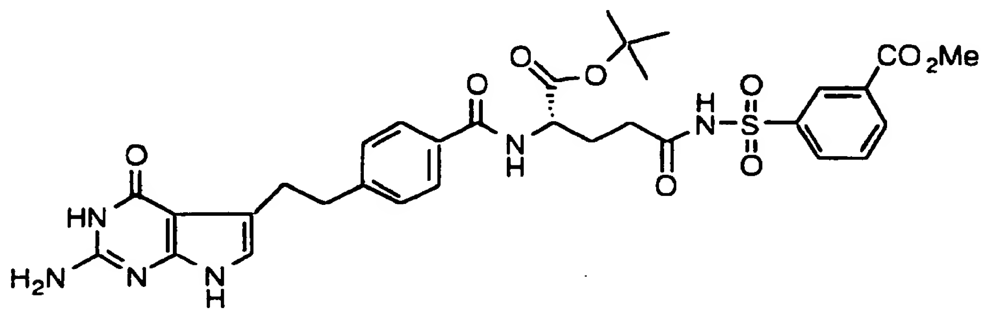
Tert-butyl ester from Example 17, Step 2 (149 mg, 0.22 mmol) and trifluoroacetic acid (5 mL) were stirred for 1 hours at RT. The reaction was concentrated in vacuo, and the crude product was purified by column chromatography (5% H_2O/5% AcOH/CH_3CN to 10% H_2O/5% AcOH/CH_3CN) to give the product as an off-white solid (132 mg, 97%).

^{1}H NMR (DMSO-d_6) δ 10.62 (s, NH), 10.17 (s, NH), 8.45 (d, J = 7.52 Hz, NH), 8.13 (d, J = 8.3 Hz, ArH_2), 8.01 (d, J = 8.42 Hz, ArH_2), 7.76 (d, J = 8.22 Hz, ArH_2), 7.28 (d, J = 7.99 Hz, ArH_2), 6.31 (s, PyrH), 6.03 (br s, NH_2), 4.30-4.22 (m, CH), 3.00-2.82 (m, CH_2CH_2), 2.40 (t, J = 6.6 Hz, CH_2), 2.04-1.97 (m, C$\underline{H}$H), 1.87-1.80 (m, CH$\underline{H}$) ppm; IR (KBr) υ_{max} 3370, 1696, 1640, 1536, 1179, 1085 cm^{-1}; UV (EtOH) λ_{max} 228.0 (ε = 32834) nm; MS (FAB) m/z 611 (M^{+1}, 5).

Example 18

Synthesis of γ-3-carboxyphenylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid

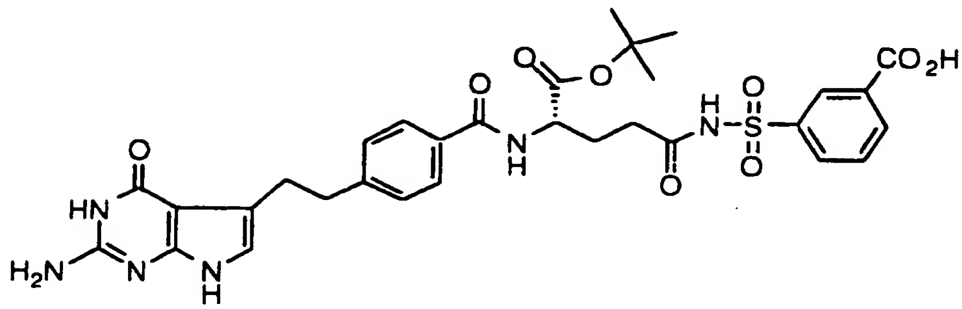
Step 1: **Synthesis of γ-t-butyl-γ-3-carboxymethylphenylsulfonamyl-N-4-[(2-amino-3H-4- xo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl glutamate:**



Carboxylic acid from Preparation 6 (500 mg, 1.03 mmol) and methyl 3-(aminosulfonyl)benzoate (668 mg, 3.10 mmol) were reacted according to the Sulfonamide Coupling Procedure of Preparation 7 for 18 hours to give the product as a white solid (273 mg, 39%).

^{1}H NMR (DMSO-d_6) δ 10.61 (s, NH), 10.14 (s, NH), 8.46-8.39 (m, NH, ArH), 8.22 (d, J = 7.68 Hz, ArH), 8.14 (d, J = 7.43 Hz, ArH), 7.79-7.68 (m, ArH_3), 7.26 (d, J = 7.93 Hz, ArH_2), 6.30 (s, PyrH), 5.99 (s, NH_2), 4.18-4.11 (m, CH), 3.90 (s, CH_3), 2.99-2.79 (m, CH_2CH_2), 2.36 (t, J = 7.26 Hz, CH_2), 1.94-1.71 (m, CH_2), 1.36 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3366, 1728, 1662, 1635, 1534, 1439, 1301, 1271, 1154 cm^{-1}; UV (EtOH) λ_{max} 222 (ε = 37876) nm; MS (FD) m/z 680 (M^+, 88).

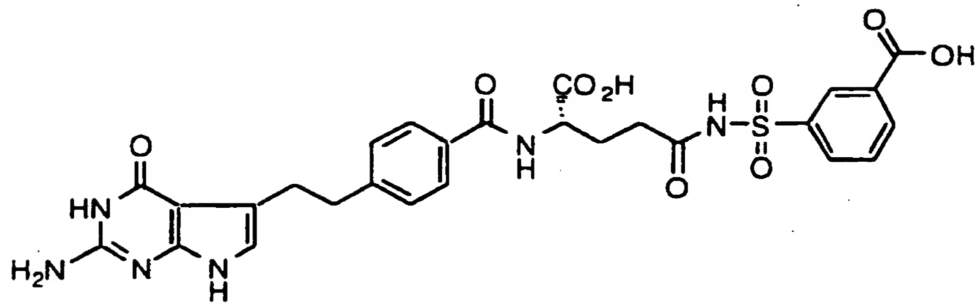
Step 2: **Synthesis of γ-t-butyl-γ-3-carboxyphenylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid:**



A solution of methyl ester (241 mg, 0.354 mmol) and 1N aqueous LiOH (0.88 mL, 0.88 mmol) in dioxane/H_2O (15 mL) was stirred at 100°C for 4 hours The reaction was cooled, concentrated to small volume, acidified to pH 2 and the resulting solid was filtered. The crude product was purified by flash chromatography (0.5% AcOH/15% MeOH/CH_2Cl_2) to give the product as a white solid (111 mg, 47%).

^1H NMR (DMSO-d_6) δ 10.61 (s, NH), 10.20 (br s, NH), 8.89 (d, J = 5.66 Hz, NH), 8.34 (s, ArH), 7.96 (d, J = 7.57 Hz, ArH), 7.89 (d, J = 7.62 Hz, ArH), 7.73 (d, J = 8.05 Hz, ArH_2), 7.44 (t, J = 7.75 Hz, ArH), 7.23 (d, J = 8.04 Hz, ArH_2), 6.31 (s, PyrH), 6.03 (br s, NH_2), 4.11-4.05 (m, CH), 2.98-2.78 (m, CH_2CH_2), 2.13-2.05 (m, CH_2), 1.92-1.79 (m, CH_2), 1.37 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3358, 1636, 1546, 1437, 1394, 1370, 1155 cm^{-1}; UV (MeOH) λ_{max} 221.5 (ε = 32377) nm; MS (FAB) *m/z* 667 (M^{+1}, 7);

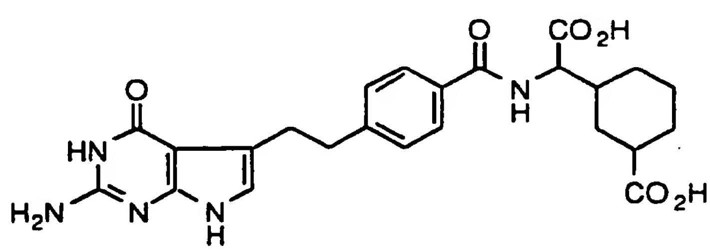
<u>Step 3:</u> Synthesis of γ-3-carboxyphenylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid:



Tert-butyl ester from Example 18, Step 1 (78 mg, 0.12 mmol) and trifluoroacetic acid (3 mL) were stirred for 1 hour at RT. The reaction was concentrated in vacuo, and the crude product was sonicated in AcOH/CH_3CN, centrifuged and dried to give the product as a green solid (65 mg, 91%).

^{1}H NMR (DMSO-d_6) δ 10.61 (s, NH), 10.15 (s, NH), 8.46 (d, J = 8.05 Hz, NH), 8.42 (s, ArH), 8.21 (d, J = 8.23 Hz, ArH), 8.12 (d, J = 7.52 Hz, ArH), 7.80-7.72 (m, ArH_3), 7.27 (d, J = 8.01 Hz, ArH_2), 6.30 (s, PyrH), 6.00 (s, NH_2), 4.29-4.23 (m, CH), 3.00-2.82 (m, CH_2CH_2), 2.43-2.35 (m, CH_2), 2.03-1.80 (m, CH_2) ppm; IR (KBr) υ_{max} 3355, 1693, 1639, 1536, 1502, 1441, 1345, 1180 cm^{-1}; UV (MeOH) λ_{max} 222.75 (ε = 30604) nm; MS (FAB) m/z 611 (M^{+1}, 5).

Example 19



Active ester (100 mg, 0.25 mmol) and dimethyl DL-3-carboxycyclohexylglycinate (116 mg, 0.51 mmol) in

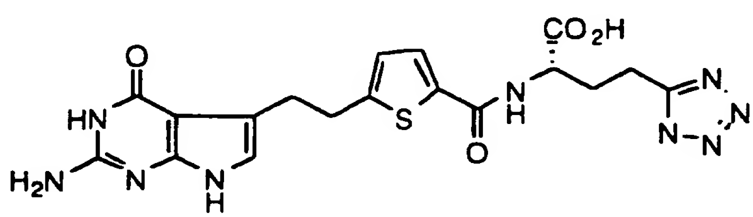
dimethylformamide (2 mL) were stirred for 17 hours at 50°C. The reaction was concentrated and purified by flash chromatography (10% $MeOH/CH_2Cl_2$) to give the desired intermediate product as a white solid (61 mg, 47%); MS (FD) *m/z* 509 (M^+, 100).

The resulting dimethyl ester precursor of the above-depicted compound (61 mg, 0.12 mmol) was reacted with 1N aqueous NaOH (0.36 mL, 0.36 mmol) in dioxane (3 mL) and H_2O (2 mL) at 50°C for 4 hours The reaction was concentrated and the crude product was sonicated with 1N aqueous HCl and the resulting solid was filtered, washed with H_2O, Et_2O and dried to give the product as a green solid (43 mg, 74%).

^1H NMR (DMSO-d_6) δ 11.08 (br s, NH), 11.02 (br s, NH), 8.39-8.32 (m, NH), 7.78 (d, J = 7.77 Hz, ArH_2), 7.27 (d, J = 8.09 Hz, ArH_2), 6.41 (s, PyrH), 4.31-4.25 (m, CH), 2.96-2.83 (m, CH_2CH_2), 2.22-2.13 (m, CH), 1.93-1.01 (m, $4CH_2$, CH) ppm; IR (KBr) υ_{max} 3390, 2930, 1685, 1536, 1503, 1216 cm^{-1}; UV (EtOH) λ_{max} 203.5 (ε = 33617), 224.5 (ε = 24060) nm; MS (FAB) *m/z* 482 (M^{+1}, 22).

Example 20

Synthesis of γ-tetrazole-N-{2-[2-methyl-3H-4-oxo-pyrrolo[2,3-d]-pyrimidin-5-yl)eth-2-yl]thiophen-5-yl}-carbonyl-L-glutamic acid

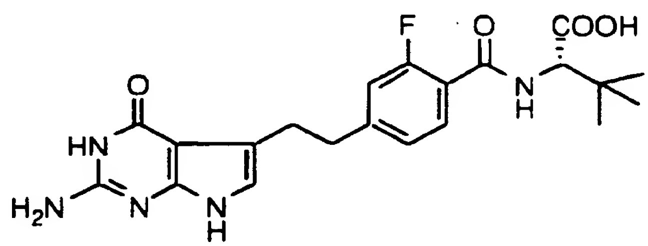


The active ester from Preparation 2, Step 3 (50 mg, 0.124 mmol) and L-(γ-tetrazole) glutamic acid (118 mg, 0.623 mmol) were reacted according to General Procedure 5A for 16 hours to give the product as a white solid (18 mg, 30%).

^1H NMR (DMSO-d_6) δ 10.62 (s, NH), 10.14 (s, NH), 8.60 (d, J = 7.79 Hz, NH), 7.63 (d, J = 3.50 Hz, ArH), 6.81 (d, J = 3.52 Hz, ArH), 6.33 (s, PyrH), 5.98 (s, NH_2), 4.36-4.30 (m, CH), 3.20-3.05 (m, CH_2), 2.95-2.85 (m, CH_2), 2.80-2.70 (m, CH_2), 2.30-2.09 (m, CH_2) ppm; IR (KBr) υ_{max} 3336, 3220, 2928, 1631, 1544, 1523, 1457 cm^{-1}; UV (EtOH) λ_{max} 221.75 (ε = 22246), 279.50 (ε = 21947) nm; MS (FAB) *m/z* 458 (M^{+1}, 95).

Example 21

Synthesis of N-{2-Fluoro-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl] benzoyl}-L-tert-leucine:



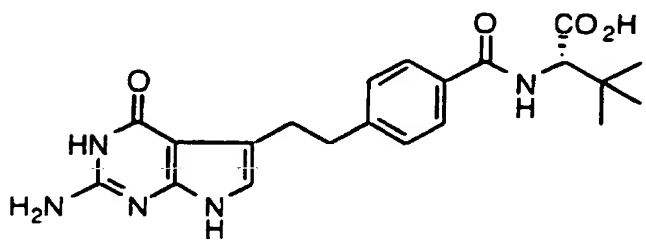
The active ester from Preparation 3, Step 4 (50 mg, 0.13 mmol), and L-tert-leucine (95 mg, 0.73 mmol) were reacted according to General Procedure 5B for 20 hours to give the product as a tan solid (38 mg, 49%).

^1H NMR (DMSO-d_6) δ 10.86 (s, NH), 10.59 (s, NH), 8.09 (dd, J = 8.66, 4.38 Hz, NH), 7.52 (t, J = 7.68 Hz, ArH), 7.20-7.05 (m, ArH_2), 6.62-6.30 (br s, NH_2), 6.40 (s, PyrH), 4.31 (d, J = 8.68 Hz, CH), 3.05-2.85 (m, CH_2CH_2), 1.02 (s, 3 CH_3) ppm;

IR (KBr) υ_{max} 3340, 3335, 3240, 2965, 2872, 1670, 1624, 1529, 1495, 1422, 1226 cm^{-1}; MS (FAB) *m/z* 430 (M^{+1}, 55).

Example 22

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-L-tert-leucine:

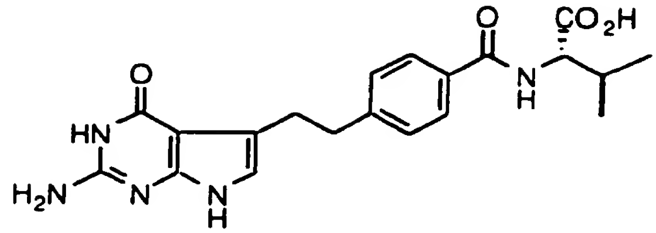


Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and L-tert-leucine (50 mg, 0.38 mmol) were reacted according to General Procedure 5C for 16 hours to give the product as a blue solid (46 mg, 88%).

^{1}H NMR (DMSO-d_6) δ 11.23 (br s, 2NH), 8.03 (d, J = 8.78 Hz, NH), 7.76 (d, J = 7.92 Hz, ArH_2), 7.26 (d, J = 8.00 Hz, ArH_2), 6.45 (s, PyrH), 4.33 (d, J = 8.73 Hz, CH), 2.95-2.82 (m, CH_2CH_2), 1.02 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3242, 2968, 2765, 1697, 1672, 1525, 1502, 1375, 1225, 1077 cm^{-1}; UV (EtOH) λ_{max} 203 (ε = 33542), 224.5 (ε = 22407), 246.5 (ε = 17576) nm; MS (FAB) *m/z* 412 (M^{+1}, 27).

Example 23

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-L-valine:



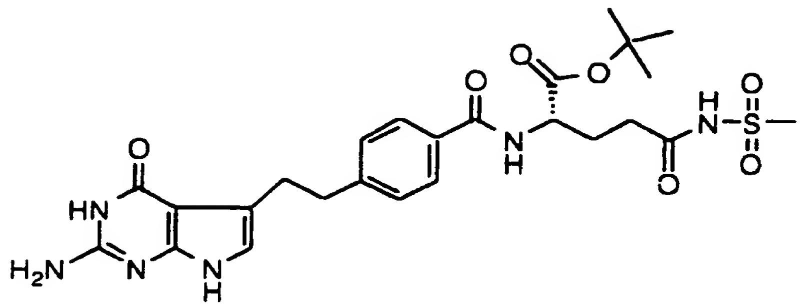
Active ester from Preparation 4, Step 4 (200 mg, 0.51 mmol) and L-valine (178 mg, 1.52 mmol) were reacted according to General Procedure 5A for 16 hours to give the product as a light green solid (120 mg, 60%).

^1H NMR (DMSO-d_6) δ 10.83 (br s, NH), 8.30 (d, J = 8.46 Hz, NH), 7.79 (d, J = 8.09 Hz, ArH_2), 7.28 (d, J = 8.09 Hz, ArH_2), 6.38 (s, PyrH), 4.30-4.24 (m, CH), 3.00-2.83 (m, CH_2CH_2), 2.28-2.15 (m, CH), 0.97 (d, J = 6.62 Hz, CH_3), 0.95 (d, J = 5.15 Hz, CH_3) ppm; IR (KBr) υ_{max} 3244, 2760, 1675, 1528, 1501, 1413, 1225, 1192, 1072 cm^{-1}; UV (MeOH) λ_{max} 202.5 (ε = 33724), 224.5 (ε = 23094) nm; MS (FAB) m/z 398 (M^{+1}, 85).

Example 24

Synthesis of γ-methylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid:

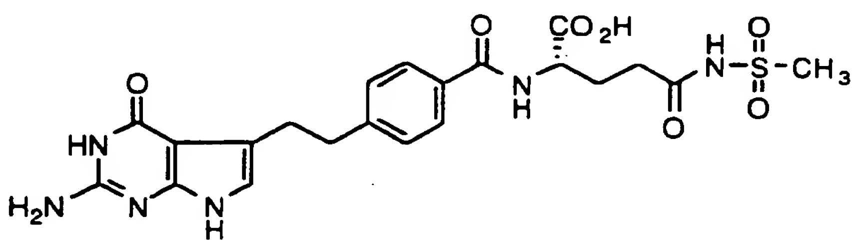
Step 1: **Synthesis of γ-t-butyl-γ-methylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-glutamate:**



Carboxylic acid from Preparation 6 (3.0 g, 6.20 mmol) and methanesulfonamide (1.77 g, 18.6 mmol) were reacted according to the Sulfonamide Coupling Procedure of Preparation 7 for 14 hours to give the product as a white solid (1.33 g, 38%).

^1H NMR (DMSO-d_6) δ 10.60 (br s, NH), 10.14 (s, NH), 8.53 (d, J = 7.49 Hz, NH), 7.77 (d, J = 8.06 Hz, ArH_2), 7.28 (d, J = 8.26 Hz, ArH_2), 6.29 (s, PyrH), 5.99 (br s, NH_2), 4.31-4.24 (m, CH), 3.17 (s, CH_3), 3.01-2.81 (m, CH_2CH_2), 2.40 (t, J = 7.38 Hz, CH_2), 2.09-1.86 (m, CH_2), 1.40 (s, $3CH_3$) ppm.

<u>Step 2:</u> Synthesis of γ-methylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid:



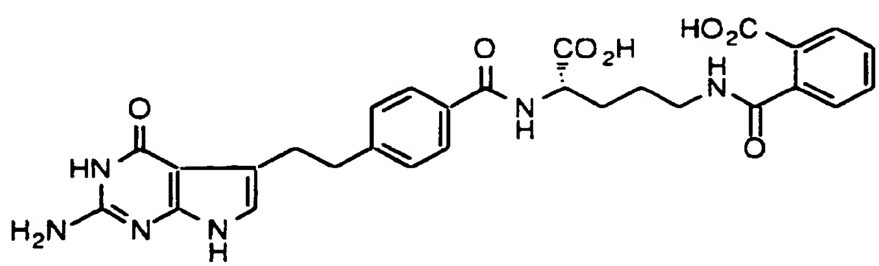
Tert-butyl ester from Example 24, Step 1 (150 mg, 0.40 mmol) and trifluoroacetic acid (3 mL) were stirred for 3 hours at RT. The reaction was concentrated in vacuo, and the crude product was sonicated in 1N HCl, filtered, washed

with H_2O and Et_2O and dried to give the product as an off-white solid (28 mg, 14%).

^1H NMR (DMSO-d_6) δ 11.68 (s, NH), 11.17 (br s, NH), 8.51 (d, J = 7.69 Hz, NH), 7.78 (d, J = 7.81 Hz, ArH_2), 7.28 (d, J = 8.13 Hz, ArH_2), 6.43 (s, PyrH), 4.40-4.33 (m, CH), 3.20 (s, CH_3), 2.96-2.80 (m, CH_2CH_2), 2.41 (t, J = 7.13 Hz, CH_2), 2.18-1.91 (m, CH_2) ppm; IR (KBr) υ_{max} 3391, 2705, 1697, 1670, 1505, 1436, 1326, 1132, 1092 cm^{-1}; MS (FAB) *m/z* 505 (M^{+1}, 6).

Example 25

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl L-ornithine

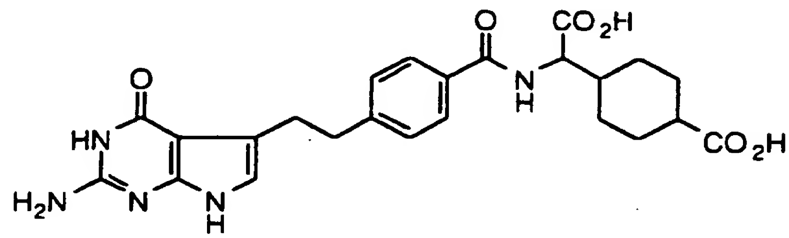


To a solution of phthalimide-protected amine (see Example 44 *supra*) (65 mg, 0.12 mmol) in dimethylsulfoxide (1 mL) was added 2.5 N aqueous NaOH (0.2 mL) dropwise over 1 minute. The reaction was stirred at RT for 5 min, diluted with H_2O, acidified to pH 2 with 1N HCl and the resulting solid was filtered, washed with H_2O and Et_2O and dried to give the product as a white solid (49 mg, 73%).

^1H NMR (DMSO-d_6) δ 10.60 (s, NH), 10.13 (s, NH), 8.49 (d, J = 7.51 Hz, NH), 8.28 (t, J = 5.85 Hz, NH), 7.78 (d, J = 8.08 Hz, ArH_2), 7.74 (d, J = 7.31 Hz, ArH), 7.57-7.45 (m, ArH_2), 7.39 (d, J = 7.18 Hz, ArH), 7.27 (d, J = 8.03 Hz, ArH_2), 6.30 (s, PyrH), 5.99 (s, NH_2), 4.38-4.32 (m, CH), 3.23-3.14

(m, CH_2), 2.99-2.80 (m, CH_2CH_2), 1.90-1.54 (m, $2CH_2$) ppm; IR (KBr) υ_{max} 3318, 2933, 1689, 1638, 1539, 1503, 1440, 1307, 1233 cm^{-1}; UV (EtOH) λ_{max} 224 (ε = 33377) nm; MS (FAB) *m/z* 561 (M^{+1}, 7).

Example 26

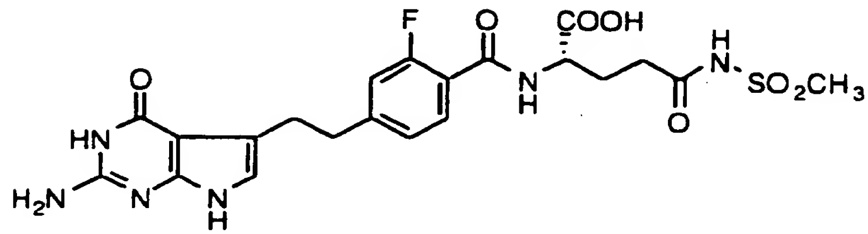


Active ester (100 mg, 0.25 mmol) and dimethyl DL-4-carboxycyclohexylglycinate (117 mg, 0.51 mmol) in dimethylformamide (2 mL) were stirred for 20 hours at 75°C. The reaction was concentrated and purified by flash chromatography (10% MeOH/CH_2Cl_2) to give the dimethyl ester of the above depicted compound as an off white solid (33 mg, 25%). MS (FD) *m/z* 509 (M^+, 100).

The resulting dimethyl ester (130 mg, 0..25 mmol) was reacted with 2.5N aqueous NaOH (0.4 mL) in dimethyl sulfoxide (2 mL) at RT for 1 hours The reaction was acidified and the resulting solid was filtered, washed with H_2O, Et_2O and dried to give the compound drawn above as a white solid (93.5 mg, 76%).

^1H NMR (DMSO-d_6) δ 10.60 (s, NH), 10.14 (s, NH), 8.39 (d, J = 8.12 Hz, 0.5 NH), 8.33 (d, J = 7.94 Hz, 0.5 NH), 7.77 (dd, J = 2.71, 8.13 Hz, ArH_2), 7.26 (d, J = 8.07 Hz, ArH_2), 6.30 (s, PyrH), 6.00 (s, NH_2), 4.31 (t, J = 8.16 Hz, 0.5 CH), 4.23 (t, J = 7.43 Hz, 0.5 CH), 2.98-2.81 (m, CH_2CH_2), 1.93-1.10 (m, $4CH_2$, 2CH) ppm; IR (KBr) υ_{max} 3335, 2934, 2861, 1638, 1533, 1502, 1343, 1227 cm^{-1}; UV (EtOH) λ_{max} 224 (ε = 22605) nm; MS (FAB) *m/z* 482 (M^{+1}, 35).

Example 27

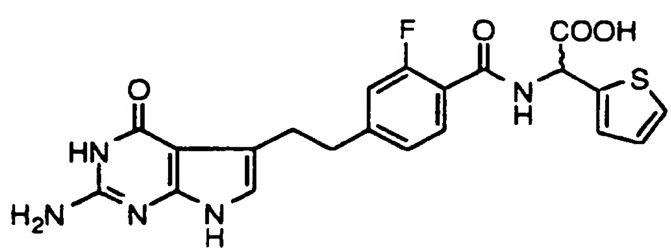


The active ester (50 mg, 0.13 mmol), and methyl sulfonamide (150 mg, 0.67 mmol) were reacted according to General Procedure 5B for 20 hours to give the product as a brown solid (35 mg, 55%).

^{1}H NMR (DMSO-d_6) δ 11.72 (s, NH), 11.09 (s, NH), 10.99 (br s, NH), 8.40 (dd, J = 7.39, 5.31 Hz, NH), 7.60-7.52 (m, ArH), 7.35-6.75 (br s, NH), 7.16-7.00 (m, ArH_2), 6.44 (s, PyrH), 4.42-4.30 (m, CH), 3.22 (s, CH_3), 3.00-2.76 (m, CH_2CH_2), 2.40-2.32 (m, CH_2), 2.25-1.86 (m, CH_2) ppm; IR (KBr) υ_{max} 3385, 2714, 1705, 1667, 1508, 1422, 1332, 1145, 1088 cm^{-1}; MS (FAB) m/z 523 (M^{+1}, 68).

Example 28

Synthesis of γ-amino-N-{2-Fluoro-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]}-benzoyl-2-thiophene-acetic acid



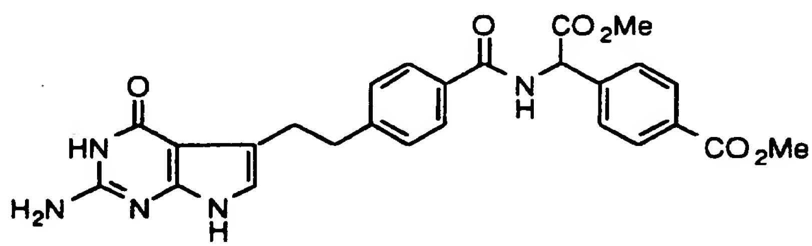
The active ester from Preparation 3, Step 4 (75 mg, 0.18 mmol), and DL-α-amino-2-thiopheneacetic acid (114 mg, 0.73 mmol) were reacted according to General Procedure 5B for 20 hours to give the product as a brown solid (40 mg, 61%).

^{1}H NMR (DMSO-d_6) δ 10.92 (s, NH), 10.69 (s, NH), 8.92 (dd, J = 6.82, 3.55 Hz, NH), 7.57 (t, J = 7.78 Hz, ArH), 7.51 (d, J = 4.63 Hz, ArH), 7.30-7.00 (m, ArH_4), 6.41 (s, PyrH), 5.78 (d, J = 7.26 Hz, CH), 3.00-2.80 (m, CH_2CH_2) ppm; IR (KBr) υ_{max} 3160, 2925, 1692, 1668, 1622, 1517, 1491, 1421, 1380, 1227 cm^{-1}; MS (FAB) *m/z* 456 (M^{+1}, 85).

Example 29

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-4-carboxyphenylglycine

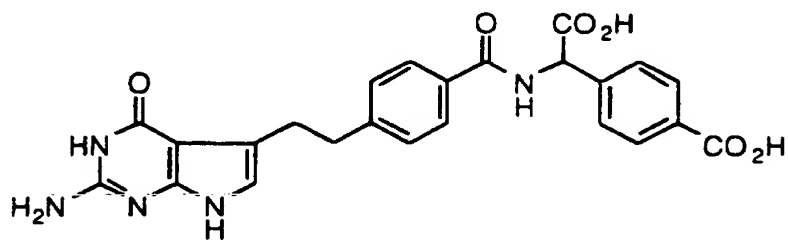
Step 1: Synthesis of dimethyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-4-carboxyphenylglycinate



Active ester from Preparation 4, Step 4 (100 mg, 0.25 mmol) and dimethyl DL-4-carboxyphenyl glycinate (135 mg, 0.60 mmol) in dimethylformamide (2 mL) were stirred for 16 hours at 50°C, then 20 hours at 75°C. The reaction was concentrated and purified by flash chromatography (5% $MeOH/CH_2Cl_2$, changing to 15% MeOH) to give the product as an off white solid (97 mg, 76%). [^{1}H NMR (DMSO-d_6) δ 10.60 (br s, NH), 10.13 (br s, NH), 9.21 (d, J = 7.33 Hz, NH), 7.96

(d, J = 8.22 Hz, ArH_2), 7.81 (d, J = 8.11 Hz, ArH_2), 7.62 (d, J = 8.33 Hz, ArH_2), 7.28 (d, J = 8.12 Hz, ArH_2), 6.29 (s, PyrH), 5.99 (br s, NH_2), 5.79 (d, J = 7.3 Hz, CH), 3.85 (s, CH_3), 3.66 (s, CH_3), 3.00-2.83 (m, CH_2CH_2) ppm; MS (FD) *m/z* 504 (M^+, 100)]

Step 2: Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-4-carboxyphenylglycine



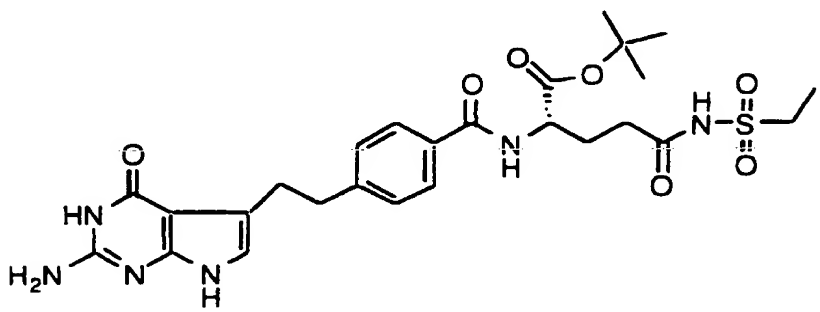
The dimethyl ester from Example 29, Step 1 (95 mg, 0.19 mmol) was reacted with 1N aqueous NaOH (0.57 mL, 0.57 mmol) in dioxane (3 mL) and H_2O (2 mL) at RT for 3 hours The reaction was concentrated and the crude product was sonicated with 1N aqueous HCl and the resulting solid was filtered, washed with H_2O, Et_2O and dried to give the product as a green solid (69 mg, 77%).

^1H NMR (DMSO-d_6) δ 10.78 (br s, NH), 10.51 (br s, NH), 9.03 (d, J = 7.46 Hz, NH), 7.92 (d, J = 8.03 Hz, ArH_2), 7.81 (d, J = 7.92 Hz, ArH_2), 7.60 (d, J = 8.05 Hz, ArH_2), 7.27 (d, J = 8.01 Hz, ArH_2), 6.34 (s, PyrH), 5.68 (d, J = 7.36 Hz, CH), 2.98-2.79 (m, CH_2CH_2) ppm; IR (KBr) υ_{max} 3330, 1690, 1528, 1497, 1378, 1262, 1183, 1116, 1078, 1019 cm^{-1}; UV (EtOH) λ_{max} 202.5 (ε = 52514), 227 (ε = 29683), 243.5 (ε = 30754) nm; MS (FAB) *m/z* 476 (M^{+1}, 8).

Exampl 30

Synthesis of γ-ethanesulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]-pyrimidin-5-yl)eth-2-yl]benzoyl-glutamic acid:

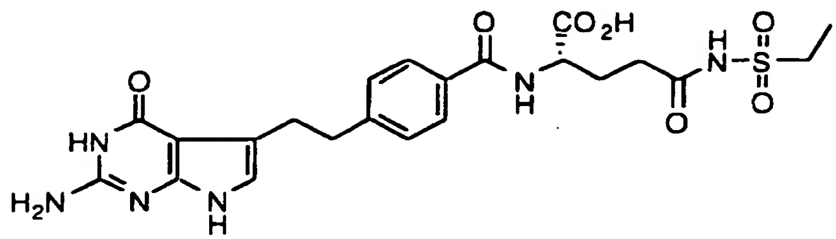
Step 1: Synthesis of γ-t-butyl-γ-ethanesulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]-pyrimidin-5-yl)eth-2-yl]benzoyl-glutamate:



Carboxylic acid from Preparation 6 (400 mg, 0.83 mmol) and ethanesulfonamide (271 mg, 2.48 mmol) were reacted according to the Sulfonamide Coupling Procedure of Preparation 7 for 18 hours to give the product as a white solid (198 mg, 42%).

^{1}H NMR (DMSO-d_6) δ 11.58 (br s, NH), 10.61 (br s, NH), 10.13 (s, NH), 8.51 (d, J = 7.41 Hz, NH), 7.77 (d, J = 8.03 Hz, ArH_2), 7.28 (d, J = 8.06 Hz, ArH_2), 6.30 (s, PyrH), 5.99 (br s, NH_2), 4.31-4.26 (m, CH), 3.34-3.27 (m, CH_2), 3.01-2.81 (m, CH_2CH_2), 2.42 (t, J = 7.25 Hz, CH_2), 2.09-1.89 (m, CH_2), 2.09-1.89 (m, CH_2), 1.40 (s, $3CH_3$), 1.17 (t, J = 7.32 Hz, CH_2) ppm.

Step 2: Synthesis of γ-ethanesulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]-pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid:



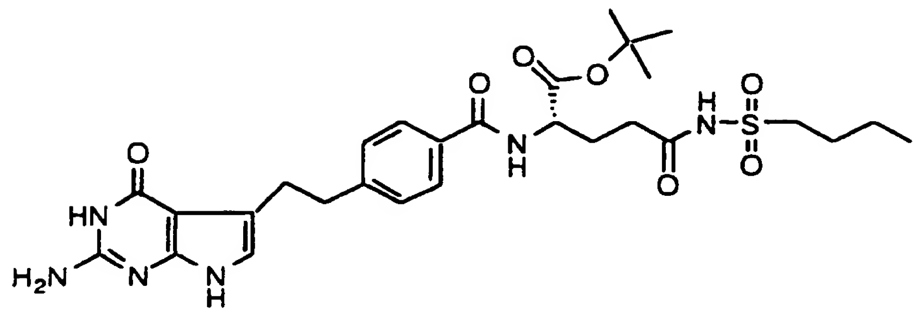
Tert-butyl ester from Example 30, Step 1 (175 mg, 0.30 mmol) and trifluoroacetic acid (5 mL) were stirred for 1 hour at RT. The reaction was concentrated in vacuo, and the crude product was purified by column chromatography (5% AcOH/ 5% H_2O/ CH_3CN) to give the product as an off-white solid (81 mg, 51%).

^1H NMR (DMSO-d_6) δ 10.60 (s, NH), 10.20 (s, NH), 8.61-8.55 (m, NH), 7.77 (d, J = 7.95 Hz, ArH_2), 7.26 (d, J = 8.0 Hz, ArH_2), 6.29 (s, PyrH), 6.03 (s, NH_2), 4.25-4.20 (m, CH), 3.07-2.81 (m, $3CH_2$), 2.21 (t, J = 6.90 Hz, CH_2), 2.04-1.88 (m, CH_2), 1.07 (t, J = 7.35 Hz, CH_3) ppm; IR (KBr) υ_{max} 3354, 1636, 1540, 1502, 1438, 1410, 1337, 1134 cm^{-1}; UV (MeOH) λ_{max} 223.0 (ε = 22697) nm; MS (FAB) m/z 519 (M^{+1}, 3).

Example 31

Synthesis of γ-n-butylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]-pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid

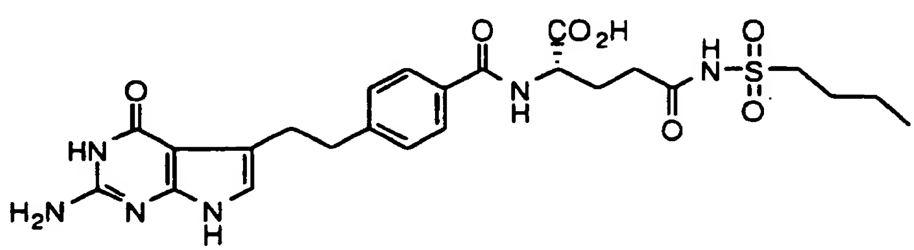
Step 1: Synthesis of γ-t-butyl-γ-n-butylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]-pyrimidin-5-yl)eth-2-yl]benzoyl glutamate:



Carboxylic acid (400 mg, 0.83 mmol) and n-butylsulfonamide (340 mg, 2.48 mmol) were reacted according to the Sulfonamide Coupling Procedure of Preparation 7 for 16 hours to give the product as a white solid (199 mg, 40%).

^{1}H NMR (DMSO-d_6) δ 11.60 (br s, NH), 10.61 (br s, NH), 10.13 (br s, NH), 8.50 (d, J = 7.43 Hz, NH), 7.77 (d, J = 7.81 Hz, ArH_2), 7.28 (d, J = 7.93 Hz, ArH_2), 6.30 (s, PyrH), 5.99 (br s, NH_2), 4.32-4.25 (m, CH), 3.31-3.24 (m, CH_2), 2.97-2.79 (m, CH_2CH_2), 2.45-2.37 (m, CH_2), 2.08-1.87 (m, CH_2), 1.64-1.52 (m, CH_2), 1.40 (s, $3CH_3$), 1.37-1.27 (m, CH_2), 0.85 (t, J = 7.17 Hz, CH_3) ppm; IR (KBr) υ_{max} 3361, 2962, 2934, 1664, 1635, 1533, 1453, 1369, 1338, 1155 cm^{-1}; UV (EtOH) λ_{max} 223 (ε = 25094) nm; MS (FD) m/z 602 (M^{+}, 64).

<u>Step 2:</u> Synthesis of γ-n-butylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]-pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid:

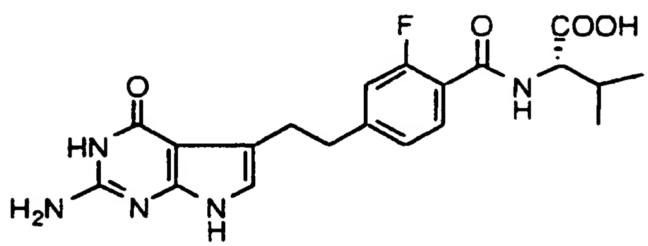


Tert-butyl ester from Example 31, Step 1 (161 mg, 0.27 mmol) and trifluoroacetic acid (5 mL) were stirred for 1 hour at RT. The reaction was concentrated in vacuo, and the crude product was sonicated in AcOH/CH_3CN, centrifuged and dried to give the product as a green solid (133 mg, 91%).

^1H NMR (DMSO-d_6) δ 11.58 (s, NH), 10.73 (s, NH), 10.40 (br s, NH), 8.46 (d, J = 7.79 Hz, NH), 7.78 (d, J = 8.0 Hz, ArH_2), 7.28 (d, J = 8.0 Hz, ArH_2), 6.34 (s, PyrH), 4.40-4.25 (m, CH), 3.32 (dd, J = 6.18, 8.99 Hz, CH_2), 2.99-2.79 (m, CH_2CH_2), 2.43 (t, J = 7.12 Hz, CH_2), 2.15-2.06 (m, C$\underline{H}$H), 1.95-1.86 (m, CH$\underline{H}$), 1.64-1.52 (m, CH_2), 1.39-1.29 (m, CH_2), 0.85 (t, J = 7.27 Hz, CH_3) ppm; IR (KBr) υ_{max} 3360, 2961, 2935, 1636, 1539, 1502, 1450, 1336, 1133 cm^{-1}; UV (MeOH) λ_{max} 223.0 (ε = 25015) nm; MS (FAB) *m/z* 547 (M^{+1}, 100).

Example 32

Synthesis of N-{2-Fluoro-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)-eth-2-yl]}-benzoyl-L-valine:



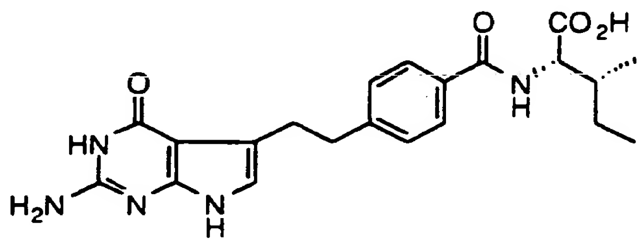
The active ester from Preparation 3, Step 4 (50 mg, 0.13 mmol), and L-valine (59 mg, 0.50 mmol) were reacted according to General Procedure 5B for 20 hours to give the product as a tan solid (39 mg, 77%).

^1H NMR (DMSO-d_6) δ 11.28 (br s, 2 NH), 8.23 (dd, J = 7.40, 2.22 Hz, ArH), 7.51 (t, J = 7.50 Hz, ArH), 7.60-7.00 (br s, NH_2), 7.18-7.00 (m, ArH_2), 6.49 (s, PyrH), 4.31 (t, J = 6.33

Hz, CH), 3.05-2.76 (m, CH_2CH_2), 2.32-2.01 (m, CH), 0.94 (d, J = 5.39 Hz, 2 CH_3) ppm; IR (KBr) υ_{max} 3457, 3244, 1736, 1699, 1674, 1623, 1525, 1202 cm^{-1}; MS (FAB) *m/z* 416 (M^{+1}, 79).

Example 33

Synthesis of allo-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-L-isoleucine:



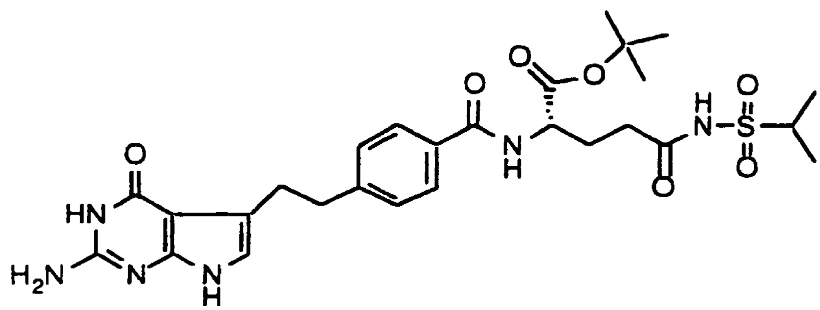
The active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol), and L-allo-isoleucine (83 mg, 0.63 mmol) were reacted according to General Procedure 5A for 16 hours to give the product as a light blue solid (41 mg, 79%).

^1H NMR (DMSO-d_6) δ 11.04 (s, NH), 10.96 (s, NH), 8.19 (d, J = 8.46 Hz, NH), 7.79 (d, J = 8.09 Hz, ArH_2), 7.29 (d, J = 8.09 Hz, ArH_2), 6.43 (s, PyrH), 4.54-4.50 (m, CH), 3.00-2.84 (m, CH_2CH_2), 2.05-1.93 (m, CH), 1.49-1.37 (m, CH), 1.27-1.13 (m, CH), 0.95 (d, J = 6.62 Hz, CH_3), 0.89 (t, J = 7.35 Hz, CH_3) ppm; IR (KBr) υ_{max} 3407, 3070, 2967, 1688, 1626, 1596, 1542, 1507, 1335, 1223 cm^{-1}; MS (FAB) *m/z* 412 (M^{-1}, 45).

Example 34

Synthesis of 4-isopropylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid

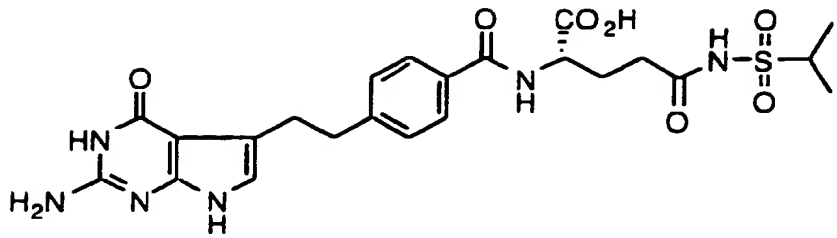
Step 1: Synthesis of γ-t-butyl-γ-4-isopropylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-glutamate:



Carboxylic acid from Preparation 6 (400 mg, 0.83 mmol) and i-propylsulfonamide (306 mg, 2.48 mmol) were reacted according to the Sulfonamide Coupling Procedure of Preparation 7 for 18 hours to give the product as a white solid (233 mg, 48%).

^{1}H NMR (DMSO-d_6) δ 10.60 (s, NH), 10.13 (s, NH), 8.56 (d, J = 7.01 Hz, NH), 7.77 (d, J = 7.99 Hz, ArH_2), 7.27 (d, J = 8.02 Hz, ArH_2), 6.30 (s, PyrH), 5.99 (br s, NH_2), 4.27-4.21 (m, CH), 3.58-3.50 (m, CH), 2.99-2.79 (m, CH_2CH_2), 2.38 (t, J = 7.05 Hz, CH_2), 2.07-1.85 (m, CH_2), 1.40 (s, $3CH_3$), 1.21 (d, J = 6.81 Hz, $2CH_3$) ppm; IR (KBr) υ_{max} 3357, 3234, 1663, 1635, 1533, 1501, 1437, 1336, 1233, 1155 cm^{-1}; UV (EtOH) λ_{max} 223.25 (ε = 27341) nm; MS (FAB) m/z 589 (M^{+1}, 18).

Step 2: Synthesis of 4-isopropylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid:

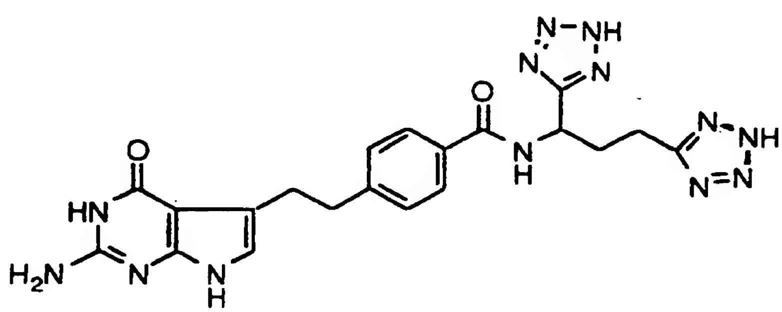


Tert-butyl ester from Example 34, Step 1 (80 mg, 0.14 mmol) and trifluoroacetic acid (2 mL) were stirred for 1 hour at RT. The reaction was concentrated in vacuo, and the crude product was sonicated in 1:1 CH_3CN/Et_2O, filtered, and dried to give the product as a green solid (63 mg, 87%).

^1H NMR (DMSO-d_6) δ 11.50 (s, NH), 11.26 (br s, NH), 8.50 (d, J = 7.73 Hz, NH), 7.78 (d, J = 8.14 Hz, ArH_2), 7.28 (d, J = 8.09 Hz, ArH_2), 6.44 (s, PyrH), 4.37-4.30 (m, CH), 3.60-3.52 (m, CH), 2.96-2.81 (m, CH_2CH_2), 2.44 (t, J = 7.33 Hz, CH_2), 2.13-2.03 (m, C<u>H</u>H), 1.93-1.83 (m, CH<u>H</u>), 1.23 (d, J = 6.83 Hz, $2CH_3$) ppm; IR (KBr) υ_{max} 3286, 1675, 1612, 1540, 1440, 1326, 1129 cm^{-1}; UV (MeOH) λ_{max} 224.0 (ε = 24160) nm; MS (FAB) *m/z* 533 (M^{+1}, 37).

Example 35

Synthesis of α,γ-bis-tetrazole-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-glutamate

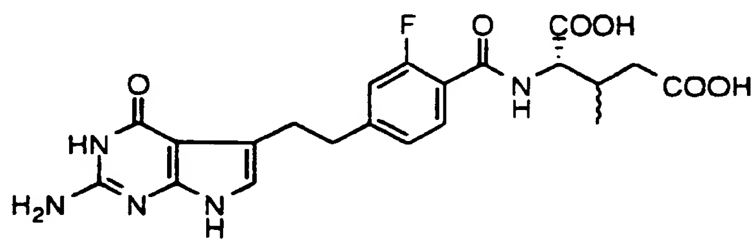


Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and DL-glutamic acid, α,γ-bistetrazole (74 mg, 0.38 mmol) were reacted according to General Procedure 5C for 80 hours to give the product as a light green solid (47 mg, 78%).

^{1}H NMR (DMSO-d_6) δ 11.20 (br s, 2NH), 9.06 (d, J = 7.77 Hz, NH), 7.82 (d, J = 7.84 Hz, ArH_2), 7.30 (d, J = 7.92 Hz, ArH_2), 6.44 (s, PyrH), 5.48-5.42 (m, CH), 3.06-2.83 (m, $3CH_2$), 2.58-2.42 (CH_2) ppm; IR (KBr) υ_{max} 3162, 2702, 2620, 1671, 1524, 1499 cm^{-1}; UV (EtOH) λ_{max} 224 (ε = 25153) nm; MS (FAB) m/z 476 (M^{+1}, 4).

Example 36

Synthesis of β-methyl-N-{2-fluoro-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]}-benzoyl-L-glutamic acid



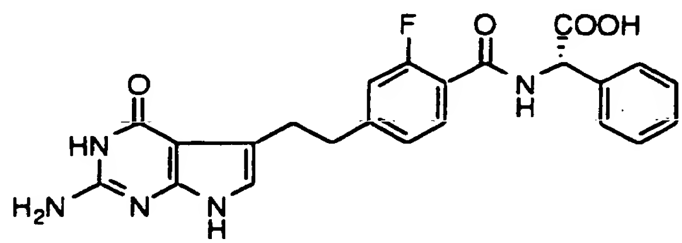
The active ester from Preparation 3, Step 4 (50 mg, 0.13 mmol), and DL-methyl glutamic acid (117 mg, 0.73 mmol) were reacted according to General Procedure 5B for 20 hours to give the product as a blue solid (21 mg, 38%). Mixture of two diastereomers, 3:2 ratio (isomer 1: isomer 2).

^{1}H NMR (DMSO-d_6) δ 10.59 (s, NH), 10.12 (s, NH), 8.24-8.13 (m, NH), 7.52-7.44 (m, ArH), 7.07 (d, J = 9.68 Hz, ArH_2), 6.29 (s, PyrH), 5.97 (s, NH_2), 4.58-4.50 (m, CH isomer 1),

4.46-4.34 (m, CH isomer 2), 3.02-2.78 (m, CH_2CH_2), 2.42-2.38 (m, CH_2), 2.35-2.18 (m, CH_2), 0.89 (dd, J = 6.70, 5.97 Hz, CH_3) ppm; IR (KBr) υ_{max} 3340, 3225, 2965, 2935, 1646, 1625, 1529, 1495, 1422, 1230 cm^{-1}; MS (FAB) m/z 460 (M^{+1}, 55).

Example 37

Synthesis of α-phenyl-N-{2-fluoro-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]}-benzoyl-glycine



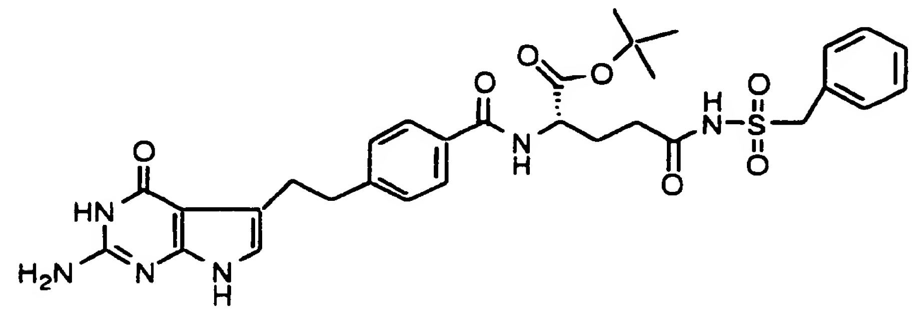
The active ester from Preparation 3, Step 4 (75 mg, 0.18 mmol), and s-phenyl glycine (110 mg, 0.73 mmol) were reacted according to General Procedure 5B for 20 hours to give the product as a tan solid (69 mg, 85%).

^{1}H NMR (DMSO-d_6) δ 13.00 (br s, CO_2H), 10.59 (s, NH), 10.12 (s, NH), 8.73 (dd, J = 4.70, 0.96 Hz, NH), 7.53-7.26 (m, ArH6), 7.15-7.00 (m, ArH2), 6.28 (s, PyrH), 5.98 (s, NH_2), 5.49 (d, J = 7.15 Hz, CH), 2.98-2.70 (m, CH_2CH_2) ppm; IR (KBr) υ_{max} 3377, 3213, 2926, 1623, 1521, 1491, 1453, 1421, 1372, 1229 cm^{-1}; MS (FAB) m/z 450 (M^{+1}, 80).

Example 38

Synthesis of γ-(α-toluenesulfonamyl)-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl]eth-2-yl]-benzoyl-L-glutamic acid:

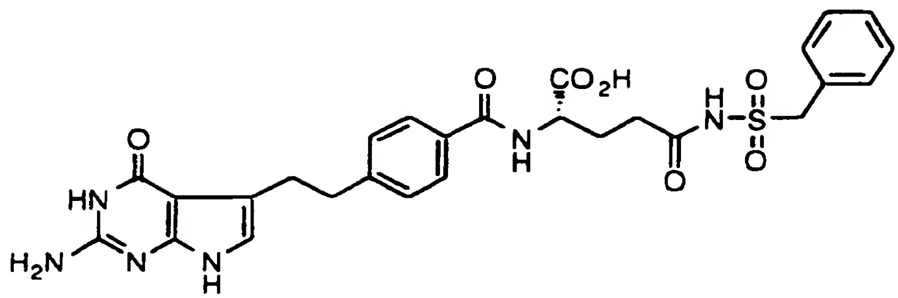
Step 1: Synth sis of α-t-butyl-γ-(α-toluenesulfonamyl)-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl]eth-2-yl]-benzoyl glutamate:



Carboxylic acid from Preparation 6 (400 mg, 0.83 mmol) and α-toluenesulfonamide (425 mg, 2.48 mmol) were reacted according to the Sulfonamide Coupling Procedure of Preparation 7 for 20 hours to give the product as a white solid (236 mg, 45%).

^1H NMR (DMSO-d_6) δ 11.56 (br s, NH), 10.61 (br s, NH), 10.14 (s, NH), 8.53 (d, J = 7.60 Hz, NH), 7.78 (d, J = 8.0 Hz, ArH_2), 7.37-7.29 (m, ArH_7), 6.30 (s, PyrH), 5.99 (br s, NH_2), 4.65 (s, CH_2), 4.39-4.30 (m, CH), 3.02-2.84 (m, CH_2CH_2), 2.37 (t, J = 7.2 Hz, CH_2), 2.18-1.90 (m, CH_2), 1.41 (s, $3CH_3$) ppm.

Step 2: Synthesis of γ-(α-toluenesulfonamyl)-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl]eth-2-yl]benzoyl-L-glutamic acid:

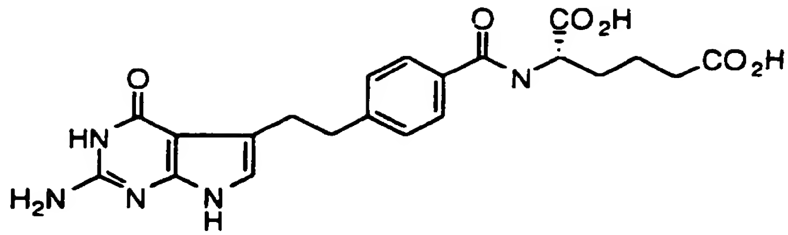


Tert-butyl ester from Example 38, Step 1 (211 mg, 0.33 mmol) and trifluoroacetic acid (5 mL) were stirred for 1 hour at RT. The reaction was concentrated in vacuo, and the crude product was sonicated in AcOH/CH_3CN, centrifuged and dried to give the product as a light blue solid (207 mg). A small sample (50 mg) was further purified by reverse-phase prep HPLC (H_2O) to give product as a white solid (14 mg, 28%).

^1H NMR (DMSO-d_6) δ 11.53 (s, NH), 10.81 (s, NH), 10.59 (br s, NH), 8.52 (d, J = 7.81 Hz, NH), 7.79 (d, J = 8.06 Hz, ArH_2), 7.37-7.27 (m, ArH_7), 6.36 (s, PyrH), 4.66 (s, CH_2), 4.44-4.37 (m, CH), 3.03-2.81 (m, CH_2CH_2), 2.38 (t, J = 7.23 Hz, CH_2), 2.24-1.91 (m, CH_2) ppm; IR (KBr) υ_{max} 3362, 1636, 1539, 1499, 1456, 1339, 1131 cm^{-1}; MS (FAB) m/z 581 (M^{+1}, 35).

Example 39

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-2-amino-L-adipic acid



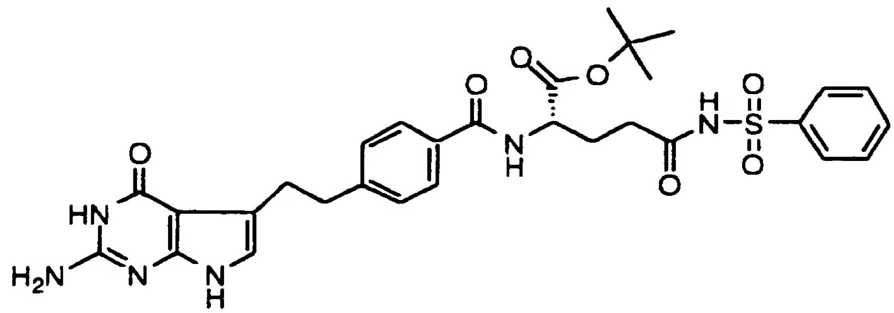
Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and 2-amino-L-adipic acid (61 mg, 0.38 mmol) were reacted according to General Procedure 5A for 18 hours to give the product as a light gray solid (32 mg, 57%).

^{1}H NMR (DMSO-d_6) δ 10.90 (s, NH), 10.73 (br s, NH), 8.50 (d, J = 7.72 Hz, NH), 7.79 (d, J = 8.09 Hz, ArH_2), 7.28 (d, J = 8.46 Hz, ArH_2), 6.39 (s, PyrH), 4.40-4.31 (m, CH), 3.00-2.82 (m, CH_2CH_2), 2.24 (t, J = 7.35 Hz, CH_2), 1.88-1.72 (m, CH_2), 1.66-1.54 (m, CH_2) ppm; IR (KBr) υ_{max} 3388, 1686, 1548, 1508, 1342, 1212, 1082 cm^{-1}; UV (MeOH) λ_{max} 203 (ε = 34599), 224.5 (ε = 23321) nm; MS (FAB) m/z 442 (M^{+}, 15).

Example 40

Synthesis of γ-4-benzenesulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid:

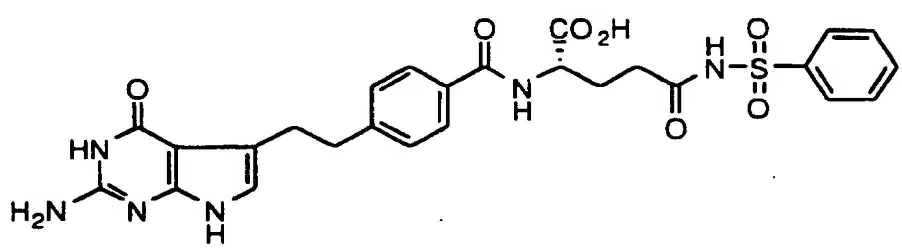
<u>Step 1:</u> **Synthesis of α-t-butyl-γ-4-benzenesulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-glutamate:**



Carboxylic acid from Preparation 6 (400 mg, 0.83 mmol) and benzenesulfonamide (390 mg, 2.48 mmol) were reacted according to the Sulfonamide Coupling Procedure of Preparation 7 for 20 hours to give the product as a white solid (200 mg, 39%).

^{1}H NMR (DMSO-d_6) δ 10.61 (s, NH), 10.14 (s, NH), 8.48 (d, J = 7.25 Hz, NH), 7.88 (d, J = 7.44 Hz, ArH_2), 7.74 (d, J = 7.99 Hz, ArH_2), 7.69-7.56 (m, ArH_3), 7.26 (d, J = 8.01 Hz, ArH_2), 6.30 (s, PyrH), 5.99 (br s, NH_2), 4.25-4.15 (m, CH), 3.01-2.82 (m, CH_2CH_2), 2.35 (t, J = 7.26 Hz, CH_2), 1.96-1.81 (m, CH_2), 1.36 (s, $3CH_3$) ppm.

<u>Step 2:</u> Synthesis of γ-4-benzenesulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid:



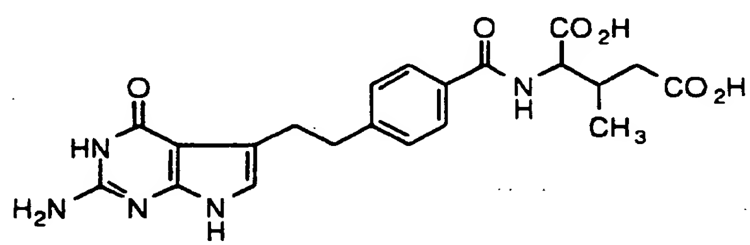
Tert-butyl ester from Example 40, Step 1 (175 mg, 0.28 mmol) and trifluoroacetic acid (4 mL) were stirred for 1 hour at RT. The reaction was concentrated in vacuo, and

the crude product was purified by column chromatography (5% H_2O/ 5% AcOH/ CH_3CN) to give the product as a light green solid (70 mg, 44%).

^{1}H NMR (DMSO-d_6) δ 10.61 (s, NH), 10.16 (s, NH), 8.61 (d, J = 6.86 Hz, NH), 7.84 (d, J = 7.34 Hz, ArH_2), 7.75 (d, J = 8.0 Hz, ArH_2), 7.58-7.48 (m, ArH_3), 7.26 (d, J = 8.07 Hz, ArH_2), 6.30 (s, PyrH), 6.01 (br s, NH_2), 4.29-4.19 (m, CH), 3.00-2.82 (m, CH_2CH_2), 2.28 (t, J = 6.9 Hz, CH_2), 1.99-1.82 (m, CH_2) ppm; IR (KBr) υ_{max} 3365, 3231, 1635, 1534, 1501, 1448, 1339, 1087 cm^{-1}; UV (MeOH) λ_{max} 222.25 (ε = 35461) nm; MS (FAB) m/z 567 (M^{+1}, 51).

Example 41

Synthesis of β-methyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidinyl-5-yl)-eth-2-yl]-benzoyl-L-glutamic acid



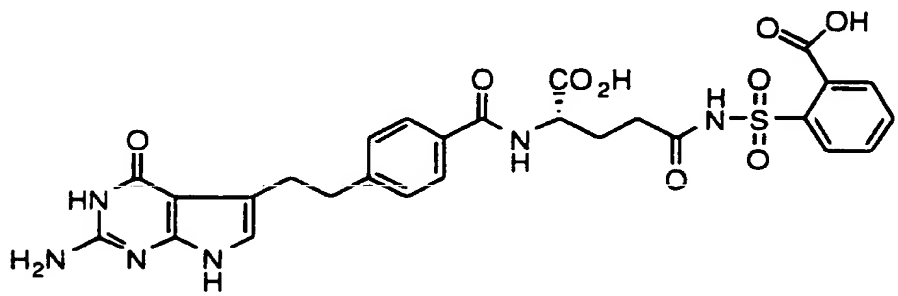
Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and DL-β-methylglutamic acid (61 mg, 0.38 mmol) were reacted according to General Procedure 5C for 18 hours to give the product as a gray solid (40 mg, 71%).

^{1}H NMR (DMSO-d_6) δ 11.25 (br s, 2NH), 8.40 (d, J = 7.99 Hz, 0.5 NH), 8.31 (d, J = 8.33 Hz, 0.5NH), 7.78 (d, J = 8.06 Hz, ArH_2), 7.27 (d, J = 8.13 Hz, ArH_2), 6.45 (s, PyrH), 4.58-4.51 (m, 0.5 CH), 4.40-4.32 (m, 0.5 CH), 2.95-2.83 (m, CH_2CH_2), 2.52-2.33 (m, CH_2), 2.26-2.03 (m, CH), 0.96 (d, J = 6.71 Hz, CH_3) ppm; IR (KBr) υ_{max} 3155, 1685, 1539, 1507,

1328, 1219, 1131, 1082 cm^{-1}; UV (EtOH) λ_{max} 202.5 (ε = 37800), 224.5 (ε = 24099) nm; MS (FAB) *m/z* 442 (M^{+1}, 14).

Example 42

Synthesis of γ-2-carboxyphenylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid



Carboxylic acid (500 mg, 1.03 mmol) and methyl 2-(aminosulfonyl)benzoate (668 mg, 3.10 mmol) were reacted according to Sulfonamide Coupling Procedure for 18 hours to give the methyl benzoate ester/pivaloate ester of the above-depicted compound as a white solid (363 mg, 51%).

^{1}H NMR (DMSO-d_6) δ 12.13 (br s, NH), 10.61 (br s, NH), 10.14 (br s, NH), 8.48-8.42 (m, NH), 8.07 (d, J = 7.88 Hz, ArH), 7.76-7.61 (m, ArH_5), 7.27 (d, J = 7.87 Hz, ArH_2), 6.30 (s, PyrH), 5.99 (br s, NH_2), 4.22-4.13 (m, CH), 3.82 (s, CH_3), 2.99-2.78 (m, CH_2CH_2), 2.43-2.35 (m, CH_2), 1.99-1.74 (m, CH_2), 1.37 (s, $3CH_3$) ppm; IR (KBr) υ_{max} 3359, 1731, 1662, 1636, 1533, 1436, 1348, 1297, 1152, 1059 cm^{-1}; UV (MeOH) λ_{max} 222 (ε = 31266) nm; MS (FD) *m/z* 681 (M^{+1}, 100);

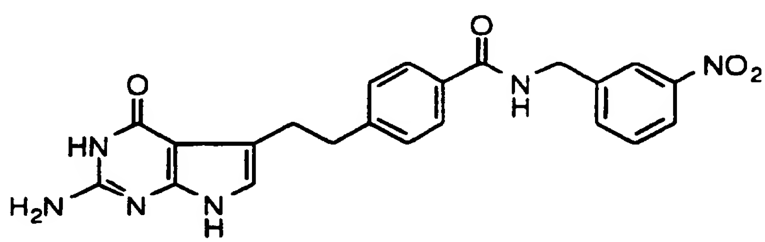
The resulting diester (50 mg, 0.08 mmol) and NaOH (2.5 N, 0.2 mL) in dimethylsulfoxide (1 mL) were stirred at RT for 45 minutes. The reaction was diluted with H_2O, acidified with 1N HCl (pH 2-3) and the solid was filtered

and dried to give the depicted product as a tan solid (29 mg, 59%).

^{1}H NMR (DMSO-d_6) δ 10.61 (s, NH), 10.15 (s, NH), 8.47 (d, J = 7.66 Hz, NH), 8.05 (d, J = 6.97 Hz, ArH), 7.80-7.64 (m, ArH_5), 7.28 (d, J = 8.14 Hz, ArH_2), 6.31 (s, PyrH), 6.01 (br s, NH_2), 4.34-4.28 (m, CH), 3.01-2.82 (m, CH_2CH_2), 2.40 (t, J = 7.0 Hz, CH_2), 2.05-1.83 (m, CH_2) ppm; IR (KBr) υ_{max} 3354, 1691, 1642, 1536, 1441, 1343 cm^{-1}; UV (EtOH) λ_{max} 223.0 (ε = 34935) nm; MS (FAB) m/z 611 (M^{+1}, 8).

Example 43

Synthesis of N-(3-nitrobenzyl)-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzamide

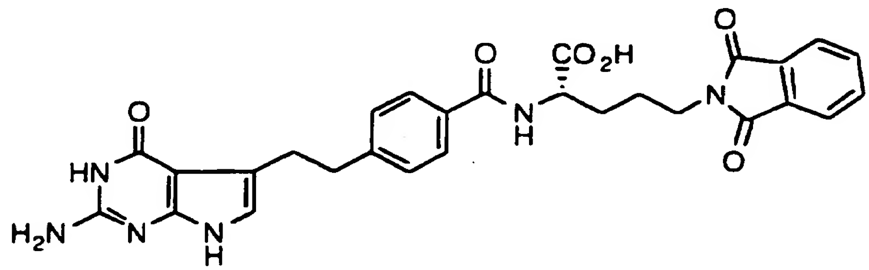


Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and 3-(aminomethyl) nitrobenzene (57 mg, 0.38 mmol) were reacted according to General Procedure 5A (except no N,O-bis(trimethylsilyl)acetamide was used) for 16 hours to give the product as an off white solid (57 mg).

^{1}H NMR (DMSO-d_6) δ 11.15-11.08 (m, 2NH), 9.16-9.09 (m, NH), 8.16 (s, ArH), 8.10 (d, J = 8.05 Hz, ArH), 7.80-7.73 (m, ArH_3), 7.62 (t, J = 7.86 Hz, ArH), 7.29 (d, J = 8.07 Hz, ArH_2), 6.44 (s, PyrH), 4.57 (d, J = 5.57 Hz, CH_2), 2.96-2.81 (m, CH_2CH_2) ppm; IR (KBr) υ_{max} 3123, 1696, 1670, 1634, 1535, 1503, 1346 cm^{-1}; UV (EtOH) λ_{max} 221 (ε = 28924), 247 (ε = 23124) nm; MS (FAB) m/z 433 (M^{+1}, 14).

Exampl 44

Synthesis of N-α-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-N-δ-phthalimido-L-ornithine



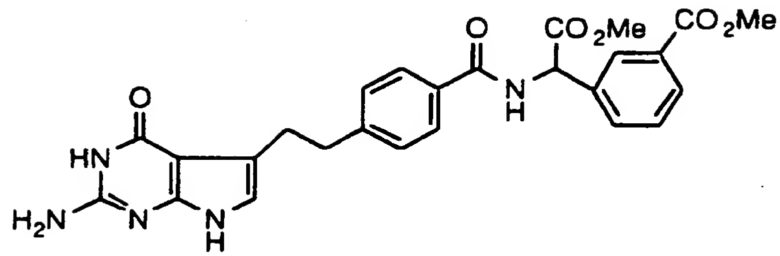
Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and N-δ-phthalimido-L-ornithine hydrochloride (113 mg, 0.38 mmol) were reacted according to General Procedure 5C for 16 hours to give the product as a yellow solid (54 mg, 78%).

^{1}H NMR (DMSO-d_6) δ 11.02 (br s, NH), 10.92 (br s, NH), 8.48 (d, J = 7.7 Hz, NH), 7.88-7.77 (m, ArH_5), 7.74 (d, J = 8.05 Hz, ArH_2), 7.25 (d, J = 8.03 Hz, ArH_2), 6.40 (s, PyrH), 4.40-4.29 (m, CH), 3.62-3.55 (m, CH_2), 2.97-2.80 (m, CH_2CH_2), 1.84-1.63 (m, $2CH_2$) ppm; IR (KBr) υ_{max} 1707, 1687, 1632, 1612, 1540, 1505, 1400 cm^{-1}; UV (EtOH) λ_{max} 220 (ε = 31873) nm; MS (FAB) *m/z* 543 (M^{+1}, 42).

Example 45

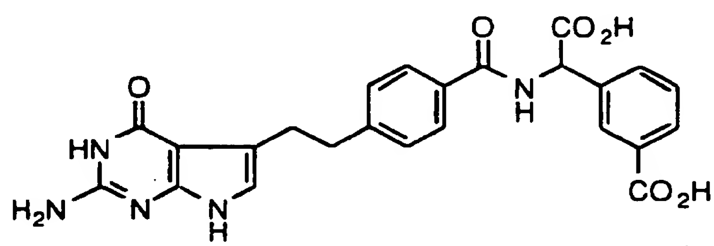
Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-3-carboxyphenylglycine:

Step 1: Synthesis of dimethyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-3-carboxyphenylglycinate:



Active ester from Preparation 4, Step 4 (100 mg, 0.25 mmol) and dimethyl DL-3-carboxyphenylglycinate (113 mg, 0.51 mmol) in dimethylformamide (2 mL) were stirred for 18 hours at 50°C. The reaction was concentrated and purified by flash chromatography (10% $MeOH/CH_2Cl_2$) to give the product as a white solid (108 mg, 85%).
[^1H NMR (DMSO-d_6) δ 10.60 (s, NH), 10.12 (s, NH), 9.22 (d, J = 7.23 Hz, NH), 8.07 (s, ArH), 7.92 (d, J = 7.65 Hz, ArH), 7.80 (d, J = 8.12 Hz, ArH_2), 7.74 (d, J = 7.64 Hz, ArH), 7.54 (t, J = 7.76 Hz, ArH), 7.27 (d, J = 8.11 Hz, ArH_2), 6.29 (s, PyrH), 5.98 (br s, NH_2), 5.77 (d, J = 7.13 Hz, CH), 3.85 (s, CH_3), 3.65 (s, CH_3), 2.96-2.80 (m, CH_2CH_2) ppm]

Step 2: Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-3-carboxyphenylglycine:



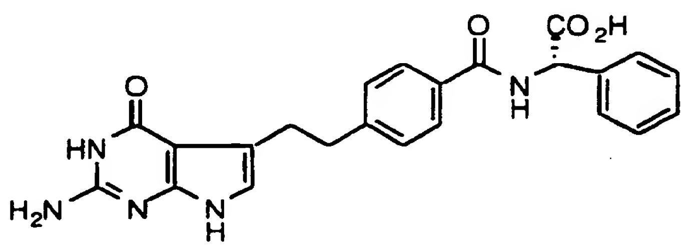
Dimethyl ester from Example 45, Step 1 (105 mg, 0.21 mmol) was reacted with 1N aqueous NaOH (0.62 mL, 0.62 mmol) in dioxane (3 mL) and H_2O (1 mL) at RT for 3 hours The reaction was concentrated and the crude product was sonicated with 1N aqueous HCl and the resulting solid was

filtered, washed with H_2O, Et_2O and dried to give the product as a light yellow solid (89 mg, 90%).

^1H NMR (DMSO-d_6) δ 10.92 (br s, NH), 10.75 (br s, NH), 9.06 (d, J = 7.47 Hz, NH), 8.05 (s, ArH), 7.88 (d, J = 7.65 Hz, ArH), 7.80 (d, J = 8.04 Hz, ArH), 7.71 (d, J = 7.53 Hz, ArH_2), 7.49 (t, J = 7.7 Hz, ArH), 7.26 (d, J = 8.14 Hz, ArH_2), 6.37 (s, PyrH), 5.66 (d, J = 7.43 Hz, CH), 2.96-2.78 (m, CH_2CH_2) ppm; IR (KBr) υ_{max} 3324, 1688, 1530, 1498, 1380, 1231, 1188, 1078, 1020 cm^{-1}; UV (EtOH) λ_{max} 203 (ε = 61583), 225.5 (ε = 34282) nm; MS (FAB) *m/z* 476 (M^{+1}, 20).

Example 46

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoylphenylglycine

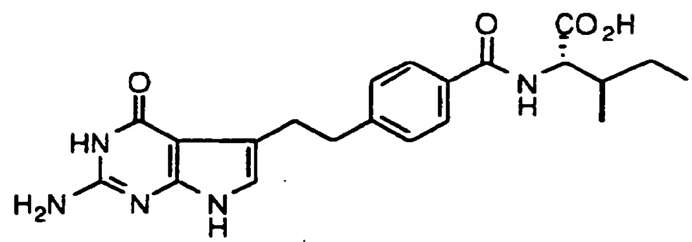


The active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol), and L-phenyl glycine (96 mg, 0.63 mmol) were reacted according to General Procedure 5A for 16 hours to give the product as an off white solid (43 mg, 78%).

^1H NMR (DMSO-d_6) δ 11.05 (s, NH), 10.96 (s, NH), 8.95 (d, J = 7.45 Hz, NH), 7.84 (d, J = 8.12 Hz, ArH_2), 7.50 (d, J = 6.77 Hz, ArH_2), 7.44-7.21 (m, ArH_5), 7.21-6.63 (Br s, NH_2), 6.42 (s, PyrH), 5.60 (d, J = 7.48 Hz, CH), 3.12-2.87 (m, CH_2CH_2) ppm; IR (KBr) υ_{max} 3142, 1682, 1528, 1495, 1377, 1074 cm^{-1}; MS (FAB) *m/z* 432 (M^{+1}, 67).

Example 47

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl]benzoyl-L-isoleucine

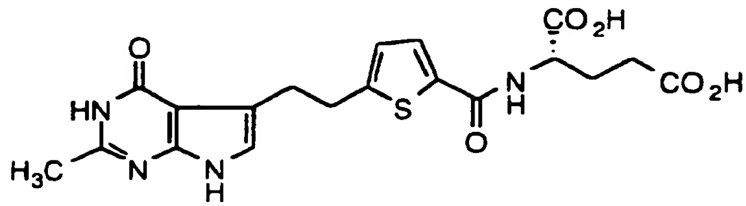


Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and L-isoleucine (50 mg, 0.38 mmol) were reacted according to General Procedure 5A for 16 hours to give the product as a pale green solid (50 mg, 96%).

^{1}H NMR (DMSO-d_6) δ 10.89 (br s, NH), 10.70 (br s, NH), 8.31 (d, J = 8.09 Hz, NH), 7.79 (d, J = 8.09 Hz, ArH_2), 7.28 (d, J = 8.09 Hz, ArH_2), 6.39 (s, PyrH), 4.34-4.29 (m, CH), 3.01-2.81 (m, CH_2CH_2), 1.99-1.89 (m, CH), 1.58-1.45 (m, C<u>H</u>H), 1.36-1.22 (m, CH<u>H</u>), 0.93 (d, J = 6.99 Hz, CH_3), 0.87 (t, J = 7.35 Hz, CH_3) ppm; IR (KBr) υ_{max} 3222, 2966, 1687, 1534, 1503, 1382, 1225, 1079 cm^{-1}; UV (MeOH) λ_{max} 202.5 (ε = 36302), 225 (ε = 23707) nm; MS (FAB) *m/z* 412 (M^{+1}, 100).

Example 48

Synthesis of N-{2-[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-yl}-carbonyl-L-glutamic acid

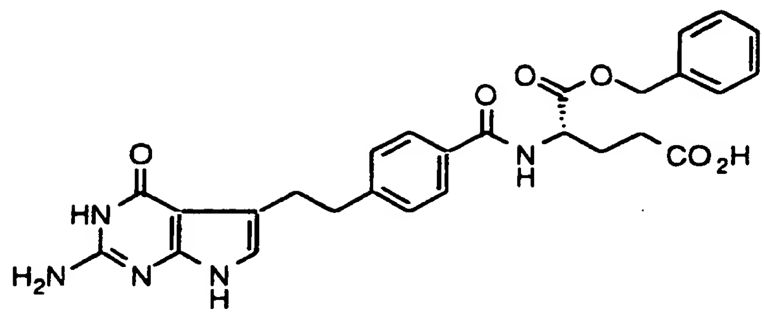


A mixture of active ester from Preparation 2, Step 3 (33 mg, 0.082 mmol) and L-glutamic acid di-t-butyl ester (127 mg, 0.49 mmol) in DMF (1 mL) was reacted according to General Procedure 5A (except no N,O-bis(trimethylsilyl)acetamide was used) for 18 hours The solvent was removed in vacuo and the crude product was dissolved in a mixture of THF (6 mL) and 1N HCl (2 mL) then refluxed for 2 hours Added 5 N HCl (2 mL) and refluxed an additional 3 hours,then stirred at RT overnight. The solvent was removed in vacuo and the crude product was sonicated with H_2O, filtered, washed with H_2O and dried to give the desired product as a dark yellow solid (12 mg, 34%).

^{1}H NMR (DMSO-d_6) δ 11.61 (br s, NH), 11.31 (br s, NH), 8.47 (d, J = 8.12 Hz, NH), 7.65 (d, J = 3.67 Hz, ArH), 6.84 (d, J = 3.27 Hz, ArH), 6.69 (s, PyrH), 4.37-4.28 (m, CH), 3.26-3.14 (m, CH_2), 3.02-2.93 (m, CH_2), 2.37-2.26 (m, CH_2), 2.28 (s, CH_3), 2.13-2.01 (m, C<u>H</u>H), 1.99-1.85 (m, CH<u>H</u>) ppm; IR (KBr) υ_{max} 3323, 2929, 2855, 1682, 1544, 1518, 1453, 1234, 1080, 815 cm^{-1}; MS (FAB) *m/z* 433 ($M^{+\cdot}$, 15).

Example 49

Synthesis of α-benzoyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoylglutamate

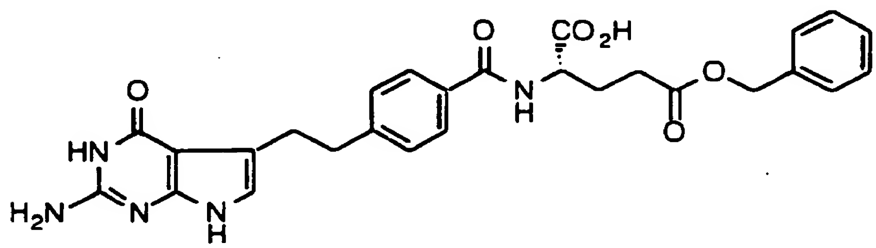


The active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol), and L-glutamic acid-α-benzylester (120 mg, 0.51 mmol) were reacted according to General Procedure 5A for 16 hours to give the product as a white solid (59 mg, 90%).

^{1}H NMR (DMSO-d_6) δ 10.89 (s, NH), 10.70 (s, NH), 8.70 (d, J = 7.72 Hz, NH), 7.79 (d, J = 8.09 Hz, ArH_2), 7.36 (s,ArH_5), 7.30 (d, J = 8.09 Hz, ArH_2), 6.39 (s, PyrH), 5.15 (s, OCH_2), 4.53-4.46 (m, CH), 3.01-2.84 (m, CH_2CH_2), 2.37 (t, J = 7.17 Hz, CH_2), 2.14-1.95 (m, CH_2) ppm; IR (KBr) υ_{max} 3234, 2756, 1701, 1669, 1537, 1500, 1358, 1224, 1077 cm^{-1}; MS (FAB) *m/z* 518 (M^{+1}, 90).

Example 50

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid γ-benzyl ester



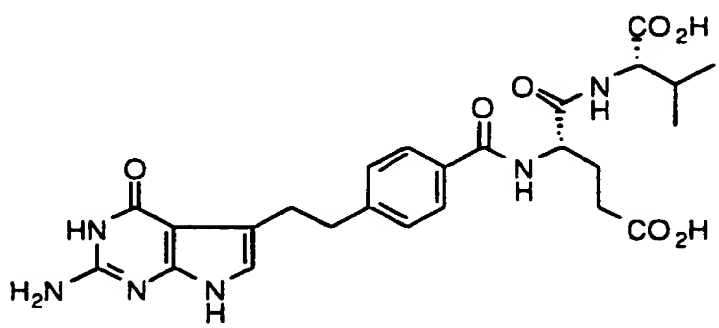
The active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol), and L-glutamic acid -γ- benzyl ester (120 mg, 0.51 mmol) were reacted according to General Procedure

5A for 16 hours to give the product as a white solid (65 mg, 99%).

^{1}H NMR (DMSO-d_6) δ 10.89 (s, NH), 10.69 (s, NH), 8.55 (d, J = 7.35 Hz, NH), 7.79 (d, J = 8.09 Hz, ArH_2), 7.35 (s, ArH_5), 7.29 (d, J = 8.09 Hz, ArH_2), 6.39 (s, PyrH, 1H), 5.09 (s, OCH_2), 4.45-4.38 (m, CH), 3.00-2.84 (m, CH_2CH_2), 2.22-1.94 (m, CH) ppm; IR (KBr) υ_{max} 3412, 3288, 3126, 2932, 2625, 1727, 1695, 1671 cm^{-1}; MS (FAB) m/z 518 (M^{+1}, 80).

Example 51

Synthesis of α-L-valine-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamate



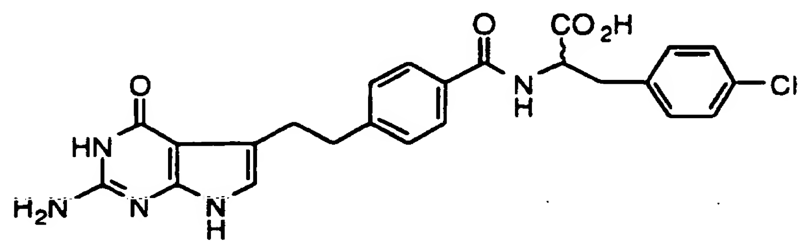
The active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol), and L-glu-α-L-val (100 mg, 0.41 mmol) were reacted according to General Procedure 5A for 16 hours to give the product as a tan solid (64 mg, 96%).

^{1}H NMR (DMSO-d_6) δ 10.88 (s, NH), 10.69 (s, NH), 8.39 (d, J = 7.72 Hz, NH), 7.98 (d, J = 8.09 Hz, NH), 7.79 (d, J = 8.09 Hz, ArH_2), 7.29 (d, J = 7.72 Hz, ArH_2), 6.39 (s, PyrH), 4.56-4.49 (m, CH), 4.17-4.12 (m, CH), 2.99-2.84 (m, CH_2CH_2), 2.34 (t, J = 7.54 Hz, CH), 2.10-1.91 (m, CH_2), 0.89 (dd, J = 2.57, 2.57 Hz, 2 CH_3) ppm; IR (KBr) υ_{max} 3236, 2747, 1723,

1700, 1667, 1540, 1373, 1224 cm^{-1}; MS (FAB) m/z 527 (M^{+1}, 60).

Example 52

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-4-chlorophenylalanine

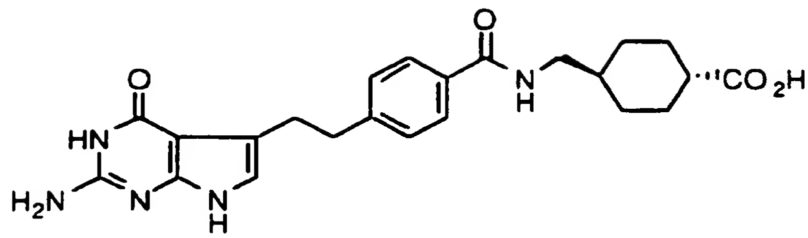


The active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol), and DL-4-chlorophenylalanine (101 mg, 0.51 mmol) were reacted according to General Procedure 5A for 16 hours to give the product as a tan solid (38 mg, 63%).

^{1}H NMR (DMSO-d_6) δ 10.89 (s, NH), 10.70 (s, NH), 8.64 (d, J = 8.46 Hz, NH), 7.71 (d, J = 8.46 Hz, ArH_2), 7.33 (s, ArH_4), 7.27 (d, J = 8.09 Hz, ArH_2), 6.64 (br s, NH_2), 6.39 (s, PyrH), 4.64-4.55 (m, CH), 3.21-3.01 (m, CH_2), 2.98-2.83 (m, CH_2CH_2) ppm; IR (KBr) υ_{max} 3162, 2928, 1671, 1534, 1493, 1439, 1227, 1091, 1015 cm^{-1}; MS (FAB) m/z 480 (M^{+1}, 85).

Example 53

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-trans-4-(aminomethyl)cyclohexane-carboxylic acid

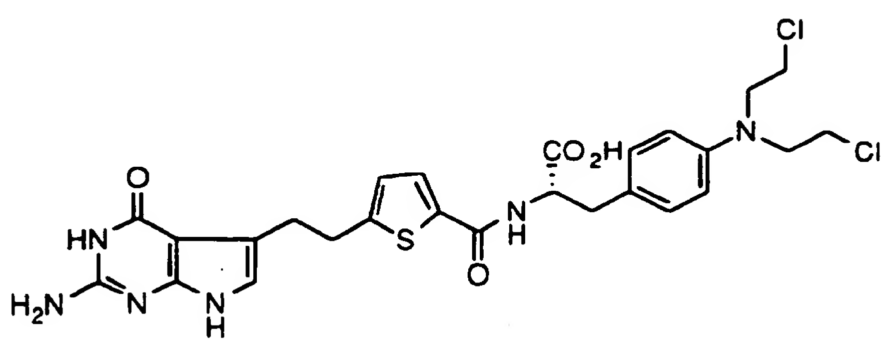


Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and *trans*-4-(aminomethyl)cyclohexane-carboxylic acid (60 mg, 0.38 mmol) were reacted according to General Procedure 5A for 16 hours to give the product as a dark red solid (53 mg, 96%).

^{1}H NMR (DMSO-d_6) δ 11.02 (s, NH), 10.90 (br s, NH), 8.38-8.31 (m, NH), 7.75 (d, J = 8.09 Hz, ArH_2), 7.27 (d, J = 8.46 Hz, ArH_2), 6.42 (s, PyrH), 3.13-3.05 (m, CH_2), 2.99-2.82 (m, CH_2CH_2), 2.19-2.06 (m, CH), 1.95-1.85 (m, CH_2), 1.84-1.71 (m, CH_2), 1.57-1.42 (m, CH), 1.33-1.16 (m, CH_2), 1.03-0.87 (m, CH_2) ppm; IR (KBr) υ_{max} 3128, 2924, 1672, 1628, 1533, 1503, 1423, 1310, 1133, 1079 cm^{-1}; UV (EtOH) λ_{max} 225 (ε = 7767) nm; MS (FAB) *m/z* 438 (M^{+1}, 10).

Example 54

Synthesis of N-(2-[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-yl)carbonyl-L-melphalan

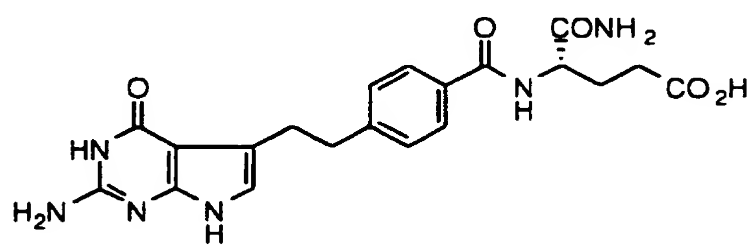


The active ester from Preparation 2, Step 3 (50 mg, 0.124 mmol), and L-melphalan (116 mg, 0.499 mmol) were reacted according to General Procedure 5A for 16 hours to give the product as a white solid (70 mg, 97%).

^1H NMR (DMSO-d_6) δ 10.68 (br s, NH), 10.25 (br s, NH), 8.54 (s, NH), 7.63 (d, ArH), 7.18 (d, ArH_2), 6.75 (d, ArH), 6.62 (d, ArH_2), 6.43 (s, PyrH), 6.04 (br s, NH_2), 4.51-4.37 (m, CH), 3.68-2.75 (m, 7 CH_2) ppm; IR (KBr) υ_{max} 3341, 2928, 1617, 1545, 1520, 1443, 1391, 1351, 1181, 1078, 813 cm^{-1}; MS (FAB) *m/z* 591 (M^{+1}, 85).

Example 55

Synthesis of N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-isoglutamate



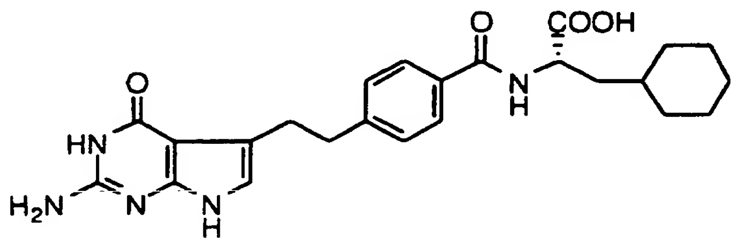
Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and L-isoglutamine (55 mg, 0.38 mmol) were reacted according to General Procedure 5C for 24 hours to give the product as a green solid (52 mg, 96%).

^1H NMR (DMSO-d_6) δ 10.66 (s, NH), 10.30 (s, NH), 8.29 (d, J = 7.85 Hz, NH), 7.79 (d, J = 7.92 Hz, ArH_2), 7.39 (s, N<u>H</u>H), 7.26 (d, J = 7.88 Hz, ArH_2), 7.04 (s, NH<u>H</u>), 6.30 (s, PyrH), 6.19 (br s, NH_2), 4.35-4.25 (m, CH), 2.98-2.78 (m, CH_2CH_2), 2.28 (t, J = 7.44 Hz, CH_2), 2.04-1.84 (m, CH_2) ppm; IR (KBr) υ_{max} 3379, 2929, 1674, 1532, 1503, 1075 cm^{-1}; UV (EtOH) λ_{max}

224.5 (ε = 4690), 241.5 (ε = 3636) nm; MS (FAB) m/z 427 (M^{+1}, 8).

Example 56

Synthesis of α-amino-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-cyclohexanepropionic acid

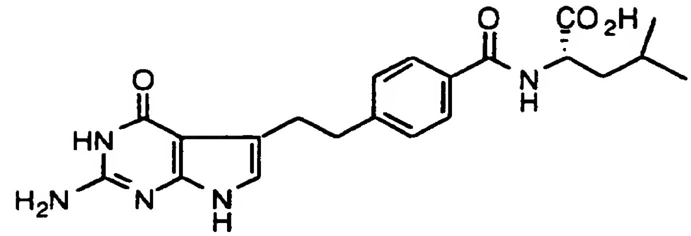


The active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol), and (s)-(-)-α-aminocyclohexane propionic acid (87 mg, 0.51 mmol) were reacted according to General Procedure 5A for 16 hours to give the product as a light blue solid (34 mg, 60%).

^{1}H NMR (DMSO-d_6) δ 10.95 (s, NH), 10.79 (s, NH), 8.49 (d, J = 7.72 Hz, NH), 7.80 (d, J = 8.09 Hz, ArH_2), 7.29 (d, J = 8.09 Hz, ArH_2), 6.75 (br s, NH_2), 6.40 (s, PyrH), 4.49-4.41 (m, CH), 2.99-2.85 (m, CH_2CH_2), 1.78-1.57 (m, $3CH_2$,CH), 1.45-1.31 (m, CH), 1.25-1.05 (m, CH_2,CH), 1.04-0.80 (m, CH_2) ppm; IR (KBr) υ_{max} 3228, 2924, 2852, 1686, 1539, 1503, 1449, 1223, 1078 cm^{-1}; MS (FAB) m/z 452 (M^{+1}, 88).

Example 57

Synthesis of 4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-L-leucine

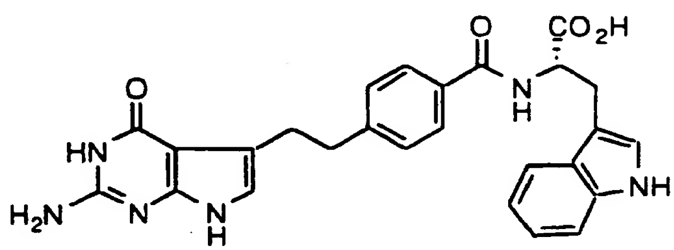


Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and L-leucine (50 mg, 0.38 mmol) were reacted according to General Procedure 5A for 18 hours to give the product as a very light green solid (39.5 mg, 76%).

^{1}H NMR (DMSO-d_6) δ 10.97 (s, NH), 10.83 (br s, NH), 8.48 (d, J = 7.72 Hz, NH), 7.79 (d, J = 8.46 Hz, ArH_2), 7.28 (d, J = 8.09 Hz, ArH_2), 6.40 (s, PyrH), 4.48-4.39 (m, CH), 3.00-2.92 (m, CH_2), 2.92-2.82 (m, CH_2), 1.83-1.52 (m, CH, CH_2), 0.92 (d, J = 6.25 Hz, CH_3), 0.88 (d, J = 6.25 Hz, CH_3) ppm; IR (KBr) υ_{max} 3180, 2958, 1687, 1538, 1504, 1438, 1226, 1079 cm^{-1}; UV (MeOH) λ_{max} 202.5 (ε = 35563), 224.5 (ε = 23046) nm; MS (FAB) m/z 412 (M^{+1}, 40).

Example 58

Synthesis of 4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]-benzoyl-L-tryptophan



Active ester from Preparation 4, Step 4 (50 mg, 0.13 mmol) and L-tryptophan (77 mg, 0.38 mmol) were reacted

according to General Procedure 5A for 18 hours to give the product as a light brown solid (48 mg, 79%).

^1H NMR (DMSO-d_6) δ 10.80 (s, NH), 10.71 (s, NH), 10.37 (br s, NH), 8.52 (d, J = 7.72 Hz, NH), 7.72 (d, J = 8.09 Hz, ArH_2), 7.59 (d, J = 7.72 Hz, ArH), 7.32 (d, J = 7.72 Hz, ArH), 7.25 (d, J = 8.46 Hz, ArH_2), 7.20 (s, PyrH), 7.09-6.96 (m, ArH_2), 6.33 (s, PyrH), 4.68-4.60 (m, CH), 3.33-3.14 (m, CH_2), 2.98-2.91 (m, CH_2), 2.89-2.81 (m, CH_2) ppm; IR (KBr) υ_{max} 3321, 2929, 1684, 1645, 1535, 1500, 1436, 1341, 1232 cm^{-1}; UV (MeOH) λ_{max} 202.5 (ε = 52411), 222 (ε = 52188) nm; MS (FAB) m/z 485 (M^{+1}, 15).

BIOLOGICAL TEST DATA

Example #	IC_{50} (µg/mL, GC3*)	Ki hTS (nM**)
1	>20	>500
2	>20	264
3	>20	>500
4	>20	>500
5	>20	>500
6	>20	>500
7	>20	>500
8	>20	>500
9	>20	>500
10	>20	>500
11	>20	46
12	>20	>500
13	>20	>500
14	12.5	>500
15	>20	8
16	>20	25
17	1.00	29
18	2.96	30
19	>20	40
20	19.2	41

21	>20	45
22	>20	46
23	>20	48
24	3.42	48
25	>20	48
26	1.90	49
27	1.50	51
28	>20	52
29	>20	53
30	2.49	55
31	NT	61
32	>20	61
33	>20	63
34	10.51	65
35	>20	68
36	3.50	69
37	6.90	73
38	NT	75
39	15.70	76
40	>20	80
41	1.00	81
42	12.66	89
43	NT	91
44	>20	102
45	>20	107
46	>20	109
47	>20	118
48	0.24	455
49	0.20	455
50	0.30	145
51	1.30	455
52	2.70	455
53	0.80	455
54	4.00	455
55	4.70	455
56	>20	454

57	>20	401
58	>20	454

*Cell Cytotoxicity for Human colon carcinoma GC3 cell lines as determined by using a MTT Colorimetric Assay. The IC_{50} was determined as the concentration of drug required to inhibit cell growth by 50%. See "Role of Membrane-Associated Folate Binding Protein in the Cytotoxicity of Antifolates in KB, IGROV1, and L1210A Cells", Schultz, et al., Oncology Research, Vol. 7, No. 2, pp 97-102, 1995, for test protocol.

**Ki is the inhibition constant for human thymidylate synthase in nanomolar(s) (nM). Test procedure for the determination of inhibition constants for thymidylate synthase as follows:

Recombinant human thymidylate synthase (HTS) expressed in E. Coli, was obtained in purified form from Dr. Daniel Santi at the University of California at San Francisco, [6R]-5,10 methylenetetrahydrofolate was obtained from Eprova AG, Switzerland. The ENZFITTER microcomputer package was purchased from Biosoft, Ferguson, MO. All additional chemicals were obtained from Sigma Chemical Company, St. Louis, MO.

The initial reaction rates, in the presence and absence of inhibitor, were determined by monitoring the increase in absorbance at 340nm resulting from formation of the product, 7,8-dihydrofolate, using a Beckman™ DU640 spectrophotometer. Assays were performed in 50 mM TES, 25 mM $MgCl_2$, 6.5 mM HCHO, 1 mM EDTA, 75 mM 2-mercaptoethanol, pH 7.4. All compounds were dissolved in DMSO to 10 mM and subsequently diluted into the assay buffer. The final DMSO concentration never exceeded 0.5% and vehicle controls confirmed that there was no effect of DMSO at this concentration. The concentrations of dUMP, [6R]-5,10 methylenetetrahydrofolate and HTS were 100 µM, 30 µM, and 30

nM respectively. An initial screen of each compound was run at 100 nM, 1 µM and 5 µM to determine inhibitory activity. If an IC_{50} of ≤ 1µM was obtained for any compound, inhibition was assessed over a wide range of concentrations and K_{iapp} values were determined by a nonlinear fit of the data to the Morrison equation using the program ENZFITTER. K_i values were derived using the equation: $K_{iapp} = K_i(1 + [S]/K_m)$, where [S] is equal to 30 µM and K_m is equal to 8 µM.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient" means a compound of Formula III or a pharmaceutically acceptable salt or solvate thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Active ingredient	250
Cellulose, micro crystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

Tablets, each containing 60 mg of active ingredient, are made as follows:

	Quantity (mg/tablet)
Active ingredient	60
Starch	45
Micro crystalline cellulose	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl starch	4.5
Magnesium stearate	0.5
Talc	1
Total	150

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl

starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 4

Capsules, each containing 80 mg of active ingredient, are made as follows:

	Quantity (mg/capsule)
Active ingredient	80
Starch	59
Micro crystalline cellulose	59
Magnesium stearate	2
Total	200

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 5

Suppositories, each containing 225 mg of active ingredient, are made as follows:

	Quantity (mg/unit)
Active ingredient	225
Saturated fatty acid glycerides	2,000
Total	2,225

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid

glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of normal 2 g capacity and allowed to cool.

Formulation 6

Suspensions, each containing 50 mg of active ingredient per 5 mL dose, are made as follows:

	Quantity (mg/unit)
Active ingredient(s)	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mL
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to total	5 mL

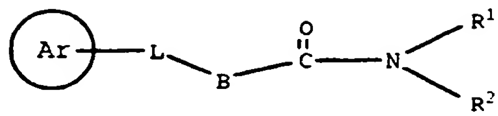
Formulation 7

An intravenous formulation may be prepared as follows:

	Quantity
Active ingredient	100 mg
Isotonic saline	1,000 mL

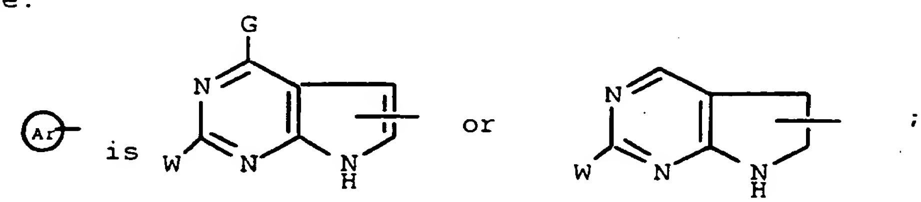
We Claim:

1. A compound of formula (III):



(III)

where:



W and G are independently -H, optionally substituted C_1-C_6 alkyl, optionally substituted aryl, $-NR^3R^4$, $-SR^5$, $-OR^6$ or halo,

R^3 and R^4 are independently -H, optionally substituted C_1-C_6 alkyl, or a suitable amino protecting group, or together N, R^3 and R^4 are a phthalimido group,

R^5 is -H, optionally substituted C_1-C_6 alkyl or a suitable thiol protecting group, and

R^6 is -H, optionally substituted C_1-C_6 alkyl or a suitable hydroxy protecting group;

L is $-R^7-Q_{(a)}-$, where

R^7 is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH{=}CH-$, $-C{\equiv}C-$, $-CH{=}CHCH_2-$, $-CH_2CH_2{=}CH-$, $-CH_2C{\equiv}C-$ and $-C{\equiv}CCH_2-$, and when R^7 is not $-C{\equiv}C-$, R^7 may be substituted with C_1-C_2 alkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 hydroxyalkyl wherein the H on the hydroxy moiety has been replaced with a hydroxy protecting group,

Q is -O-, -S- or $-NR^8$,

a is zero or 1,

R^8 is -H, optionally substituted C_1-C_3 alkyl, alkoxycarbonyl or phenoxycarbonyl;

B is selected from the group consisting of:

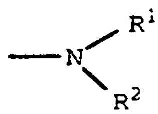
optionally substituted 1,2-, 1,3-, or 1,4-phenylene,

optionally substituted 2,3-, 2,4-, or 2,5-thienediyl,

optionally substituted 2,3-, 2,4-, or 2,5-furanediyl,

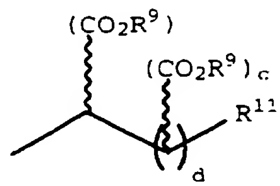
optionally substituted 1,2-, 1,3-, or 1,4-cyclohexanediyl, and

optionally substituted $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$;



is

A) an α-amino acid residue, selected from the group consisting of -alanine, -arginine, -asparagine, -aspartic acid, -cysteine, -cystine, -glutamine, -glycine, -histidine, -hydroxyproline, -isoleucine, -leucine, -lysine, -methionine, -phenylalanine, -proline, -serine, -threonine, -tryptophan, -tyrosine and -valine, **OR**

B) R^1 is 

, and R^2 is -H,

where

c is zero or 1,

d is zero, 1, 2, 3, 4, 5 or 6,

R^9 are each independently -H or a suitable carboxylic acid protecting group, and

R^{11} is

i) $-COOR^{10}$, where R^{10} is -H, optionally substituted alkyl or a suitable carboxylic acid protecting group, or

ii) -H, -OH, 1-carboxyeth-1-yl, optionally substituted C_1-C_6 alkyl, optionally substituted

cycloalkyl, carboxycycloalkyl, optionally substituted aryl, carboxyaryl, optionally substituted heteroaryl, optionally substituted alkyl(aryl), optionally substituted C_1-C_6 alkoxy, optionally substituted polycyclic, optionally substituted 5-tetrazolyl, or

ii) -$(CH_2)_e$-U

where: e is 0, 1, 2, 3 or 4,

U is -O-CH_2-COOH, -S-CH_2-COOH or -$NR^{12}R^{25}$,

R^{12} is -H or a suitable amino protecting group,

R^{25} is benzoyl or carboxybenzoyl,

or

iv) -$(CH_2)_e$-T, where

e is as above, T is phthalimido, -CO_2R^{10}, -$SO_{(g)}X$, -$NR^{13}R^{14}$, -$CONR^{13}R^{14}$, $CONHSO_2R^{15}$, -PO_3H_2 or -CO-α-amino acid residue,

R^{10} is as above,

g is zero, 1, 2 or 3, providing that when g is zero, 1 or 2, X is optionally substituted C_1-C_6 alkyl, and when g is 3, X is -H,

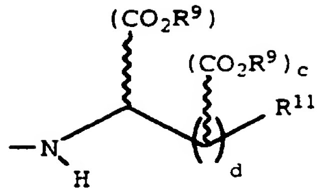
R^{13} is -H,

R^{14} is -H, optionally substituted C_1-C_6 alkyl, optionally substituted C_5-C_7 aryl, -$CHR^{16}NR^{15}R^{16}$, $\overset{O}{\overset{\|}{C}}$-aryl, or a suitable amino protecting group,

R^{15} is optionally substituted alkyl, optionally substituted aryl, benzyl or carboxyaryl, and

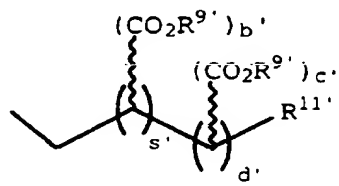
each R^{16} is independently -H or optionally substituted alkyl, and each α-amino acid residue is as above;

providing that all of R^{11} is so configured such that



is not D- or L-glutamic acid, -alanine, -arginine, -asparagine, -aspartic acid, -cysteine, -cystine, -glutamine, -glycine, -histidine, -hydroxyproline, -isoleucine, -leucine, -lysine, -methionine, -phenylalanine, -proline, -serine, -threonine, -tryptophan, -tyrosine or -valine;

OR

C) R^1 is  and R^2 is -H,

where s', b' and c' are independently zero or 1,

d' is zero, 1, 2, 3, 4, 5 or 6,

each $R^{9'}$ is independently -H or a suitable carboxylic acid protecting group,

$R^{11'}$ is

i) $-COOR^{10'}$, where $R^{10'}$ is -H, optionally substituted alkyl or a suitable carboxylic acid protecting group,

ii) -H, -OH, 1-carboxyeth-1-yl, optionally substituted C_1-C_6 alkyl, optionally substituted cycloalkyl, carboxycycloalkyl, optionally substituted aryl, carboxy aryl, optionally substituted heteroaryl, optionally substituted aryl(alkyl), optionally substituted alkoxy, optionally substituted polycyclic, optionally substituted 5-tetrazolyl, or

iii) $-(CH_2)_{e'}-U'$,

where: e' is zero, 1, 2, 3 or 4,

U' is $-O-CH_2-COOH$, $-S-CH_2-COOH$ or $-NR^{12'}R^{25'}$,

$R^{12'}$ is -H or a suitable amino protecting group,

$R^{25'}$ is benzoyl or carboxybenzoyl,

iv) $-(CH_2)_{e'}-T'$,

where e' is as above,

T' is phthalimido, $-CO_2R^{10'}$, $-SO_{(g')}X'$, $-NR^{13'}R^{14'}$, $-CONR^{13'}R^{14'}$, $-CONHSO_2R^{15'}$, $-PO_3H_2$ or -CO-α-amino acid residue, where

$R^{10'}$ is as above,

g' is zero, 2 or 3, providing that

when g' is zero or 2, X' is optionally substituted C_1-C_6 alkyl, and when g' is 3, X' is -H,

$R^{13'}$ is -H,

$R^{14'}$ is -H, optionally substituted C_1-C_6 alkyl, optionally substituted C_5-C_7 aryl, $-CHR^{16'}NR^{15'}R^{16'}$, $-\overset{O}{\overset{\|}{C}}$-aryl, or a suitable amino protecting group,

$R^{15'}$ is optionally substituted alkyl, optionally substituted aryl, benzyl or carboxyaryl, and

each $R^{16'}$ is independently -H or optionally substituted alkyl;

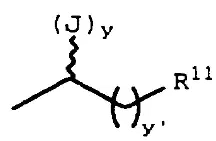
OR

D) R^1 is optionally substituted C_3-C_{20} cycloalkyl or C_3-C_{20} carboxycycloalkyl, and

R^2 is -H;

OR

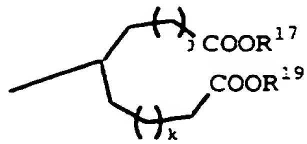
E) R^1 is



where J is optionally substituted 5-tetrazolyl or optionally substituted C_1-C_6 alkyl, y is zero or 1, y' is zero, 1, 2, 3, 4, 5 or 6 and R^{11} is as above, and

R^2 is -H;

OR

F) R^1 is  , and R^2 is -H,

where

j is zero, or an integer from 1 to 10,

k is zero, or an integer from 1 to 10,

R^{17} and R^{19} are independently -H or a suitable carboxylic acid protecting group;

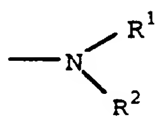
OR

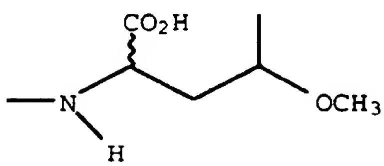
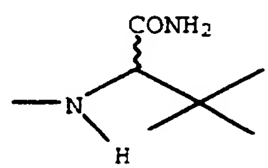
G) R^1 and R^2 are both $-(CH_2)_n-COOR^{17}$, where

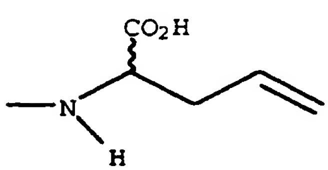
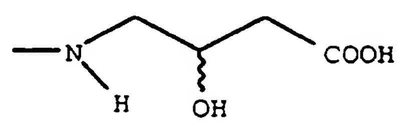
n is zero, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and

R^{17} is as defined above;

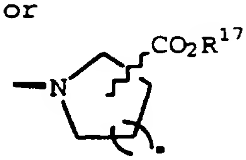
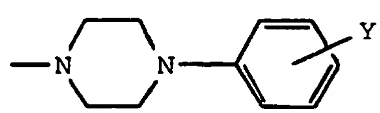
OR

H)  is:

 or  or

 or 

or

 **OR** 

where

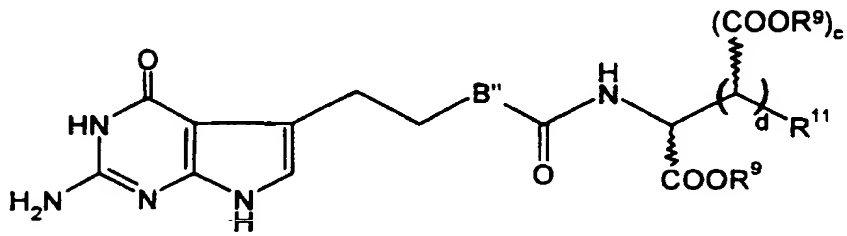
m is zero, 1 or 2,

R^{17} is as above, and

Y is selected from the group consisting of halo, nitro, amino and optionally substituted alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound of Claim 1 having the formula



wherein B" is optionally substituted phenylene or thiophenediyl or a pharmaceutically acceptable salt or solvate thereof.

3. The compound of Claim 2 which is γ-4-carboxyphenylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid or a pharmaceutically acceptable salt or solvate thereof.

4. The compound of Claim 2 which is γ-3-carboxyphenylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid or a pharmaceutically acceptable salt or solvate thereof.

5. The compound of Claim 2 which is γ-methylsulfonamyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid or a pharmaceutically acceptable salt or solvate thereof.

6. The compound of Claim 2 which is β-methyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidinyl-5-yl)-eth-2-

yl]-benzoyl-L-glutamic acid or a pharmaceutically acceptable salt or solvate thereof.

7. The compound of Claim 2 which is N-{2-[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]thiophen-5-yl}-carbonyl-L-glutamic acid or a pharmaceutically acceptable salt or solvate thereof.

8. The compound of Claim 2 which is α-benzoyl-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoylglutamate or a pharmaceutically acceptable salt or solvate thereof.

9. The compound of Claim 2 which is N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamic acid γ-benzyl ester or a pharmaceutically acceptable salt or solvate thereof.

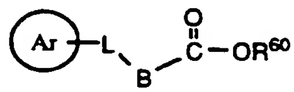
10. The compound of Claim 2 which is α-L-valine-N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-glutamate or a pharmaceutically acceptable salt or solvate thereof.

11. The compound of Claim 2 which is N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-4-chlorophenylalanine or a pharmaceutically acceptable salt or solvate thereof.

12. The compound of Claim 2 which is N-{2-[(2-methyl-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl}thiophen-5-yl}carbonyl-L-melphalin or a pharmaceutically acceptable salt or solvate thereof.

13. The compound of Claim 2 which is N-4-[(2-amino-3H-4-oxo-pyrrolo[2,3-d]pyrimidin-5-yl)eth-2-yl]benzoyl-L-isoglutamate or a pharmaceutically acceptable salt or solvate thereof.

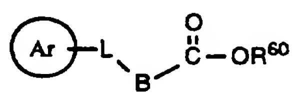
14. An active ester intermediate of formula (I):

 (I)

where , L and B have the same definitions as in Claim 1, and R^{60} is selected from the group consisting of N-hydroxysuccinimidyl, N-hydroxysulphosuccinimidyl and salts thereof, 2-nitrophenyl, 4-nitrophenyl and 2,4-dichlorophenyl.

15. The compound of Claim 14 wherein B is optionally substituted phenylene or thiophenediyl.

16. A process to make the compounds of formula (III), or pharmaceutically acceptable salts or solvates thereof, by reacting an active ester of formula (I):

 (I)

where , L and B are as defined in Claim 1, R^{60} is selected from the group consisting of N-hydroxysuccinimidyl, N-hydroxysulphosuccinimidyl and salts thereof, 2-nitrophenyl, 4-nitrophenyl and 2,4-dichlorophenyl, with an amine of formula (II):

$$HNR^1R^2 \qquad (II),$$

where R^1 and R^2 are as defined in Claim 1, in the presence of either a silylating agent or a suitable base.

17. The process of Claim 16 further comprising a rapid work-up procedure wherein a compound or salt of formula (III) is isolated and purified by the following procedure:

a) optionally adding a suitable diamine;

b) adding a suitable aqueous acid;

c) separating the product from its solvent;

d) preparing the precipitated product physically for collecting, washing and drying; and

e) collecting, washing and drying the product.

18. A pharmaceutical composition comprising a compound of Claim 1, or a pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

19. A method of treating susceptible neoplasms in a mammal in need of such treatment comprising administering a neoplasm growth inhibiting amount of a compound Claim 1, or a pharmaceutically acceptable salt or solvate thereof, to a mammal.

20. A method of treating arthritis in a mammal comprising administering an arthritis inhibiting amount of a compound of Claim 1, or a pharmaceutically acceptable salt or solvate thereof, to a mammal.

21. A method of treating psoriasis in a mammal comprising administering an psoriasis inhibiting amount of a compound of Claim 1, or a pharmaceutically acceptable salt or solvate thereof, to a mammal.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/15017

A. CLASSIFICATI N OF SUBJECT MATTER

IPC(6) :A01N 43/54; A61K 31/505; C07D 239/70, 487/00
US CL :514/258; 544/280

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/258; 544/280

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P --- A, P	US 5,644,058 A (BARNETT et al) 01 July 1997, columns 1 & 2.	1, 14-19 --- 2-13, 20, 21
A, P	US 5,661,148 A (SAKUMA et al) 26 August 1997, columns 1 & 2.	1-21
A, P	US 5,646,152 A (BRIGHT et al) 08 July 1997, columns 1 & 2.	1-21
A, P	US 5,650,511 A (ELLIOTT et al) 22 July 1997, columns 1 & 2, also drawings	1-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

02 NOVEMBER 1997

Date of mailing of the international search report

17 NOV 1997

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